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TREATMENT OF SEPTIC PATIENTS – FLUIDS, BLOOD AND TIMING OF ANTIBIOTICS

Maria Cronhjort

Karolinska Institutet

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TREATMENT OF SEPTIC PATIENTS – FLUIDS, BLOOD AND TIMING OF ANTIBIOTICS.
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Maria Cronhjort

Principal Supervisor:
Prof. Christer Svensen
Karolinska Institutet
Department of Clinical Science and Education, Södersjukhuset
Unit of Anaesthesia/Intensive Care

Co-supervisor(s):
Dr. Eva Joelsson-Alm
Karolinska Institutet
Department of Clinical Science and Education, Södersjukhuset
Unit of Anaesthesia/Intensive Care

Dr. Johan Mårtensson
Karolinska Institutet
Department of Pharmacology and Physiology
Division of Anaesthesia/Intensive Care

Opponent:
Prof. Kathy Rowan
Founder, Director of Scientific & Strategic Development and Clinical Trials Unit Director, Intensive Care National Audit & Research Centre
Honorary Professor in Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine
Honorary Professor in Division of Research Strategy, University College London
Honorary Visiting Research Fellow in Tropical Medicine, Nuffield Department of Medicine, University of Oxford

Examination Board:
Prof. Sven-Erik Ricksten
University of Gothenburg
Department of Anaesthesiology and Intensive Care
Sahlgrenska Academy, Gothenburg

Associate Prof. Miklos Lipcsey
Uppsala University
Department of Surgical Sciences
Division of Anaesthesiology and Intensive Care

Associate Prof. Peter Sackey
Karolinska Institutet
Department of Physiology and Pharmacology
Division of Anaesthesiology and Intensive Care

To my beloved soulmate and husband, Mikael.

“My soul clings to you; your right hand upholds me.”
Psalm 63:8, The Holy Bible, New International Version.

ABSTRACT

Background: Fluid therapy is an important component of the treatment of septic shock. The Surviving Sepsis Campaign recommends early fluid resuscitation with at least 30 ml/kg and there is no recommendation on when to stop giving fluids. Many studies have shown an association between fluid overload and morbidity and mortality. Clinicians base fluid prescription on variables that do not reflect fluid responsiveness.

Aim: The overall intention was to explore what scientific support there is for the treatment of septic patients in terms of their fluid management and the timing of antibiotics and to investigate new tools that could help the clinician decide on the amount and timing of blood and other fluids in septic shock.

Overview of methods:

Study	Design	Study Population	Aim	No of participants	Statistical Methods
I	RCT	Patients with septic shock and Hb ≤ 9 g/dl	To study the effect on mortality of a transfusion threshold of 7 or 9 g/dl in septic shock.	998	Logistic regression, χ^2, Wilcoxon signed-rank test
II	Cohort	Patients with septic shock and Hb ≤ 9 g/dl who survived and stayed in the ICU for three days or more	To investigate the association between the cumulative fluid balance and mortality in patients with septic shock.	841	Cox regression, χ^2, ANOVA
III	Meta-analysis	Critically ill patients	To assess whether haemodynamic optimisation by protocols reduces mortality in critically ill patients.	3323	Mantel-Haenszel random effects model
IV	RCT (pilot)	Patients with septic shock for < 12 hours	To implement a protocol based on a passive leg raising test in patients with septic shock	34	χ^2, t-test, ANOVA, Mann-Whitney U test
V	Cohort	Septic ICU patients	To describe timing of antibiotics in a cohort of septic ICU patients	210	Logistic regression, t-test, Mann-Whitney U test, Fisher's exact test

Summary of research results: The scientific support for how fluid management in patients with septic shock should be performed is poor.

- It is safe to adopt a Hb threshold of 7 g/dl in septic ICU patients except in patients with pre-existing cardiovascular disease for whom a transfusion threshold of 8 g/dl is suggested.
- It is uncertain whether fluid overload is associated with mortality at a median fluid balance of 2.5 l on day three.
- It has not been proven that protocolised haemodynamic management improves outcome.
- It was possible to use the protocol based on a passive leg raising (PLR) test, but the recruitment rate was low. The weight gain was low in both the PLR and the control groups.
- Female patients and patients with surgical sepsis were overrepresented in the group that received antibiotics after more than one hour in the emergency department. We could neither confirm nor exclude a survival benefit from early administration of antibiotics.

Keywords: septic shock, fluid therapy, randomised clinical trial, transfusion threshold, haemodynamic algorithms, meta-analysis, passive leg raising, transpulmonary thermodilution, mortality, antibiotics

LIST OF SCIENTIFIC PAPERS

I. **Lower versus higher hemoglobin threshold for transfusion in septic shock**
Holst, L. B., Haase, N, Wetterslev, J, Wernerman, J, Guttormsen, A. B, Karlsson, S, Johansson, P. I, Aneman, A, Vang, M. L, Winding, R, Nebrich, L, Nibro, H. L, Rasmussen, B. S, Lauridsen, J. R, Nielsen, J. S, Oldner, A, Pettila, V, **Cronhjort, M. B**, Andersen, L. H, Pedersen, U. G, Reiter, N, Wiis, J, White, J. O, Russell, L, Thornberg, K. J, Hjortrup, P. B, Muller, R. G, Moller, M. H, Steensen, M, Tjader, I, Kilsand, K, Odeberg-Wernerman, S, Sjobo, B, Bundgaard, H, Thyo, M. A, Lodahl, D, Maerkedahl, R, Albeck, C, Illum, D, Kruse, M, Winkel, P, Perner, A, Triss Trial Group, Scandinavian Critical Care Trials, Group.
New England Journal of Medicine 2014; 371(15): 1381-9.

II. **Association between fluid balance and mortality in patients with septic shock: a post hoc analysis of the TRISS trial**
Cronhjort M, Hjortrup PB, Holst LB, Joelsson-Alm E, Mårtensson J, Svensen C, Perner A.
Acta Anaesthesiol Scand. 2016;60(7):925-33.

III. **Impact of hemodynamic goal-directed resuscitation on mortality in adult critically ill patients: a systematic review and meta-analysis.**
Cronhjort M, Wall O, Nyberg E, Zeng R, Svensen C, Mårtensson J, Joelsson-Alm E.
Submitted.

IV. **A passive leg raising test to reduce weight gain in patients with septic shock-a randomized clinical feasibility trial.**
Cronhjort M, Bergman M, Joelsson-Alm E, Divander MB, Jerkegren E, Balintescu A, Mårtensson J, Svensen C.
Submitted.

V. **Timing of Antibiotic Treatment in a Swedish Cohort of Septic Intensive Care Patients**
Cronhjort M, Rysz S, Sandström M, Svensen C, Mårtensson J, Bell M, Joelsson-Alm E.
J Anesth Perioper Med 2015; 2: 287-94.

CONTENTS

LIST OF ABBREVIATIONS

CI	Cardiac Index
CO	Cardiac Output
CVP	Central Venous Pressure
CRF	Case Report Form
$\Delta PavCO_2$	The difference between central venous and arterial PCO2
DO_2I	Oxygen Delivery indexed to body surface
eCRF	Electronic Case Report Form
Hb	Haemoglobin concentration
HoB	Head of Bed
HR	Hazard Ratio
ICU	Intensive Care Unit
IS	Information Size
IVC	Inferior Vena Cava
MAP	Mean Arterial Pressure
MCFP	Mean Circulatory Filling Pressure
OR	Odds Ratio
PPV	Pulse Pressure Variation
QoE	Quality of Evidence
qSOFA	Quick Sequential (or Sepsis-related) Organ Failure Assessment
RAP	Right Atrial Pressure
RBC	Red Blood Cells
ROB	Risk of Bias
RR	Relative Risks
SaO_2	Oxygen saturation of Haemoglobin molecules
ScvO2	Central Venous Oxygenation
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential (or Sepsis-related) Organ Failure Assessment
SSC	Surviving Sepsis Campaign
SV	Stroke Volume

SVI	Stroke Volume Index
SVV	Stroke Volume Variation
TACO	Transfusion Associated Circulatory Overload
TPTD	Transpulmonary thermodilution
TSA	Trial Sequential Analysis

1 INTRODUCTION

A septic patient with low blood pressure, high pulse rate, high respiratory rate, cold and mottled skin and low urinary output – do they need fluids? This is an everyday clinical question that is difficult to answer solely on the basis of clinical examination and/or looking at vital parameters (1) . When working as a resident at different intensive care units in Stockholm, I experienced a wide local variation in the amount of fluids administered to patients suffering from similar diseases. A patient treated in one ICU might, after a few days, have gained ten kilograms due to fluid accumulation, whereas a patient with the same disease treated in another ICU might not have accumulated any fluid at all. I wondered whether the amount of fluids administered to patients had an impact on patient wellbeing and survival. Would it be possible to perform a test to decide whether or not a septic patient requires fluids?

Fluids are administered to septic patients in order to improve their cardiac output and thereby oxygen delivery to their cells. However, fluids appear to have negative effects such as tissue oedema, impaired renal function, impaired lung function and perhaps even increased mortality. If it was possible to test how a patient will respond to fluid, fluid administration could be restricted to those patients who will benefit from this.

This thesis is an attempt to answer a common clinical question through the application of quantitative scientific methodology.

2 BACKGROUND

2.1 WHAT IS SEPSIS?

Sepsis is a syndrome in which an infection spreads and leads to a systemic inflammation. The pathophysiology of septic shock includes vasoplegia, endothelial dysfunction with damaged glycocalyx and increased leakage (2), disturbed microcirculation (3) and often myocardial depression (4). This sometimes leads to septic shock; sepsis with insufficient oxygen delivery to different organs. A patient with septic shock has low blood pressure, high pulse rate, high respiratory rate, either warm extremities or cold, mottled skin, impaired cerebral function with confusion or agitation and low urinary output. This is a dangerous state which can occur to anyone, independent of age or past medical history. The mortality is high (40–80%) (5) .

At the beginning of this project, the common definition of septic shock was based on the systemic inflammatory response syndrome (SIRS) criteria according to a consensus document from 1991 (6). SIRS was present if two or more of the following criteria were fulfilled: 1) a body temperature > 38°C or < 36°C; 2) a heart rate > 90 beats per minute; 3) a respiratory rate > 20 breaths per minute 4) a white blood cell count > 12 x 10^9/l or < 4 x 10^9/l. Sepsis was defined as SIRS caused by infection. Septic shock was sepsis with hypotension despite adequate fluid resuscitation. However, no attempt was made to define "adequate fluid resuscitation".

Over the years, the SIRS criteria have been questioned, due both to poor sensitivity (there are clearly septic patients in the intensive care unit who do not fulfil the SIRS criteria) and poor specificity (having a cold and climbing a few stairs might be enough to fulfil the criteria for sepsis). In a retrospective evaluation of 109 663 patients with infection and organ failure, 12.1% had SIRS-negative sepsis (7). Sepsis-3 was launched in 2016, as an attempt to link the definition of sepsis to an increased risk of mortality (8). The suggested new definition of sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to an infection. Septic patients should be identified by an increase of two or more points in their Sequential Organ Failure Assessment (SOFA) score (9). SOFA is a complex scoring system that is often used in intensive care. To identify septic patients outside of the intensive care unit (ICU), a simple scoring system, Quick-SOFA (qSOFA), has been proposed: respiratory rate ≥ 22/min, systolic blood pressure ≤ 100 mmHg and altered mentation. A suspected infection and 2/3 criteria are required. Septic shock was defined as a state with serum lactate ≥ 2 mmol/l and a need for vasopressors in order to maintain a mean arterial pressure (MAP) > 65 mmHg. This would correspond to a hospital mortality > 40%.

According to the authors, the qSOFA score needs prospective validation in other settings (10). The Sepsis-3 definition has not yet been generally adopted for clinical use (11). The SIRS criteria have been used to define sepsis in the clinical trials in this project.

2.2 RED BLOOD CELL TRANSFUSIONS IN SEPSIS

Shock can be defined as a state in which oxygen delivery to the tissues is lower than their oxygen demand. This leads to organ dysfunction and is associated with anaerobic metabolism and lactate production (12). Oxygen delivery is dependent on cardiac output, haemoglobin concentration (Hb) and oxygen saturation of the haemoglobin molecules (SaO_2). Therefore, it should be possible to increase oxygen delivery by transfusing blood. However, even if the oxygen delivery is increased, it does not always follow that the cells are able to use the extra available oxygen. Transfusing red blood cells (RBC) into septic patients does not necessarily increase oxygen consumption (13-15). One possible explanation is that there was no need for increased oxygen consumption in the patients examined. Another is that the poor utilisation of oxygen in septic patients is due to mitochondrial abnormalities rather than poor delivery. A small observational study of seven children suffering from hyperdynamic shock and low oxygen extraction showed increased oxygen consumption after RBC transfusion (16). The body effectively compensates for anaemia by increasing cardiac output, redistributing blood to vital organs, increasing capillary density, making it easier for oxygen to leave the Hb molecule for the tissue, and by increasing oxygen extraction (17). It has been argued that the lack of increase in oxygen consumption after RBC transfusion is due to changes in the morphology of the RBCs because of alterations that take place during storage, which impairs flow in the smallest capillaries. Both impaired microcirculation and increased mortality after transfusion of RBCs that have been stored > 31 days have been shown (18). It is not known to what extent RBC transfusion increases oxygen consumption in septic patients who are not bleeding. It is common in intensive care for the physician to set physiological goals for each patient in the morning. The nurses then work to achieve these goals. If they are unable to reach the goal, the physician is notified. The traditional goal has been Hb > 10 g/dl, but in a recent study the median transfusion trigger was 8.3 g/dl (19). The most common negative effect of RBC transfusions is transfusion-associated circulatory overload (TACO) (1:18–1:356 events to number of transfusions) which is defined as pulmonary oedema due to volume overload (20, 21). Incompatibility reactions that occur when the wrong blood type is administered to a patient are uncommon (1:14 000-1:38 000). Other negative effects are haemolytic transfusion reactions (1:9 000) and infections (bacterial contamination 1:14 000, hepatitis C 1:1 935 000) (22). Various populations have been studied in order to determine when the possible beneficial effects outweigh the risks of negative effects. A large randomised controlled trial (RCT) of critically ill patients showed no significant difference in mortality between transfusion triggers of 7 g/dl or 10 g/dl, but in individuals with less severe illness, lower mortality was observed in the lower threshold group (23). The blood was not leukocyte-depleted, which might have resulted in more immunologic reactions. It has thus been uncertain what the optimal Hb threshold is in patients with septic shock.

2.3 WHY ADMINISTER FLUIDS IN SEPSIS?

2.3.1 Fluid responsiveness

The reason for administering fluids to septic patients is to improve cardiac output and thereby oxygen delivery. In clinical practice, however, cardiac output is not often measured. Consequently, fluids are usually administered in response to low blood pressure and high pulse rate. Preload is the stretching of the muscle cells in the left ventricle at the end of

diastole and is dependent on the volume of blood returning to the heart. The heart tries to pump out all returning blood, which means that if fluids are given, stroke volume (SV) will increase as long as the heart can increase its capacity, in accordance with Starling's law (24) . The relationship between preload and stroke volume is illustrated in a Frank-Starling curve (Fig. 1A). As both ventricles work on the steep part of the Frank-Starling curve, the heart is preload-dependent. A fluid responder is defined as a subject who manages to increase SV at increased preload, for example by 10% after 500 ml of fluid (Fig. 1B). If too much fluid is given or if the heart is failing, there will be no increase in cardiac output (Fig. 1 C). Only 50% of critically ill patients are fluid responsive (25).

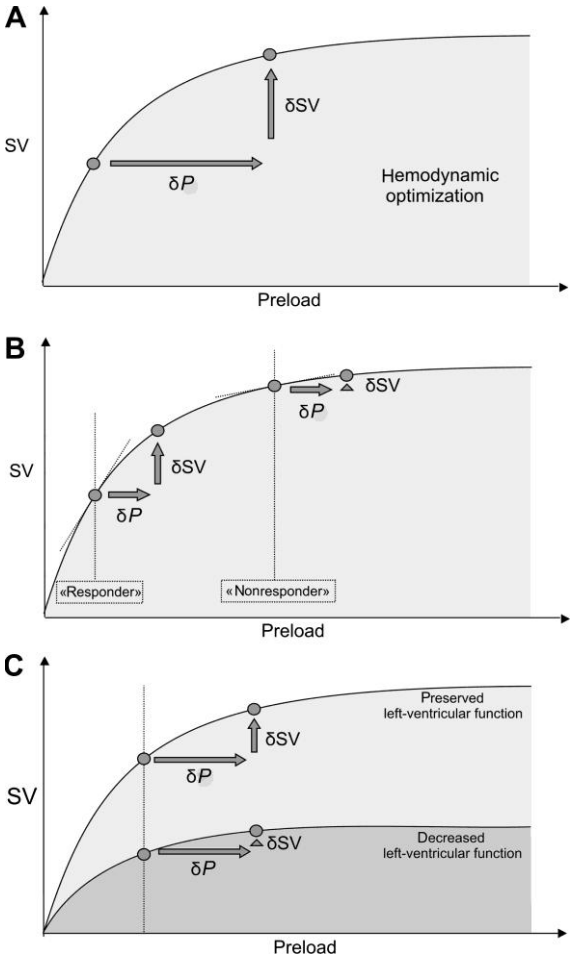

Fig. 1. The Frank-Starling curve.

A. The basis of haemodynamic optimisation: increased preload leads to increased stroke volume.

B. A fluid responder is defined as a person who manages to increase SV at increased preload, for example by 10% after 500 ml of fluid. If enough fluids are administered and preload is increased, all people will reach a point at which more fluids do not increase SV (non-responder).

C. A patient with a failing heart does not manage to increase SV, even at a low level of preload.

Reprinted from Monitoring fluid responsiveness, Hofer CK, Canneson M, Acta Anaesth Taiw, Vol 49; 2, 2011, 59–65, with kind permission from Elsevier.

2.3.2 Preload is not always increased by fluid administration

The driving pressure for venous return is the right atrial pressure (RAP) subtracted from the mean circulatory filling pressure (MCFP). MCFP is the pressure that can be measured when the heart is stopped and the arterial and venous pressures are equalised. This was conducted experimentally in dogs by Guyton et al. (26). MCFP describes the relationship between fluid volume, vascular tone and external vascular pressure. It is a measure of the elastic recoil potential in the entire circulatory system, including the heart and lungs. Venous return is also dependent on the dimensions of the vessels (which are important for the venous resistance) and the viscosity of the blood (27).

The function of venous return and cardiac function can be illustrated in the same diagram (Fig. 2) (28).

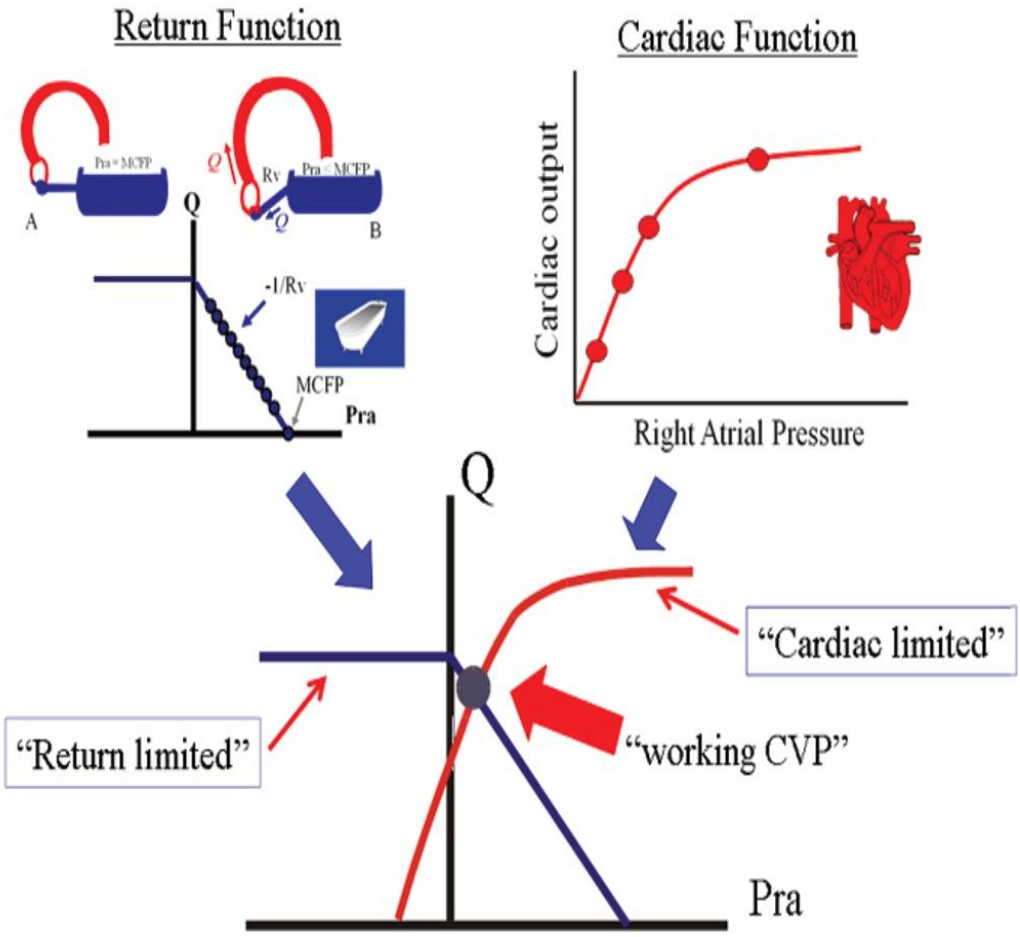

Fig. 2. Factors regulating CO according to Guyton.

The RAP (here Pra) and CO are both dependent on cardiac contractility and venous return. Q = blood flow. The driving pressure for venous return is (MCFP - RAP). Venous return is also dependent on the dimensions of the vessels and the viscosity of the blood. If there is no flow, RAP equals MCFP.

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Unstressed blood volume is the blood in the veins that does not contribute to venous return. It is the blood volume when the transmural pressure is zero. The amount of blood that has to be removed to reduce the transmural pressure to zero is the stressed blood volume. This definition is of clinical importance because hormones and drugs can change venous return by shifting the relationship between stressed and unstressed blood volumes (Fig. 3) (29).

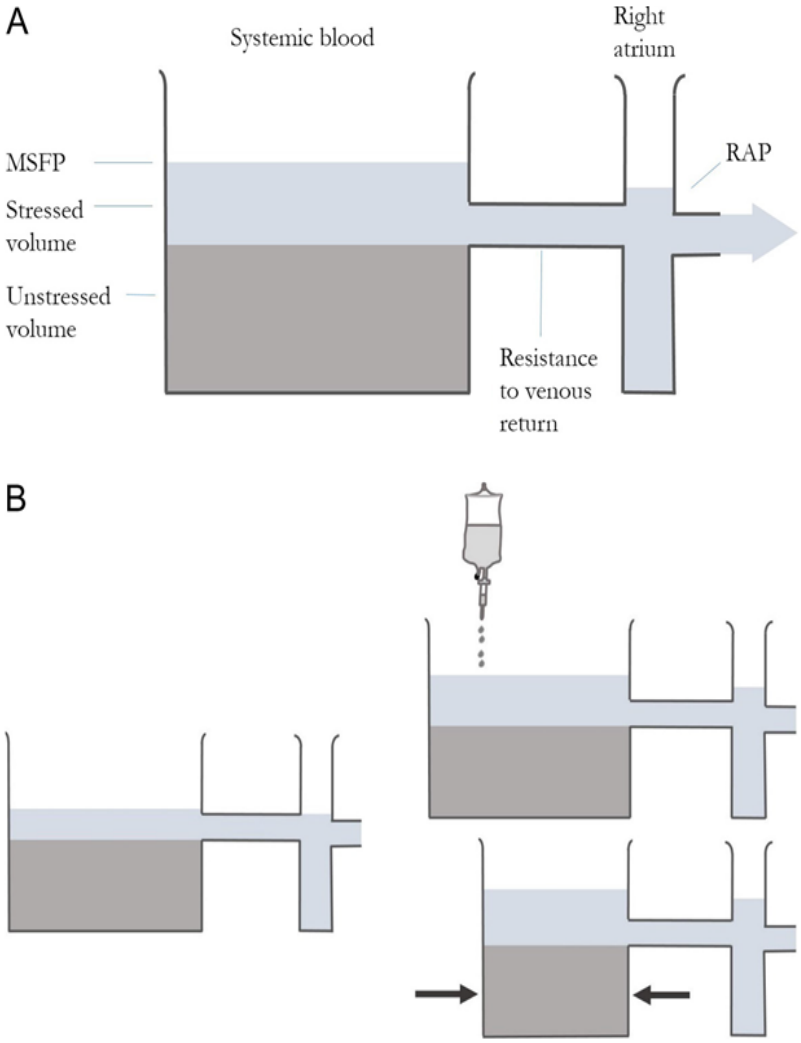

Fig. 3. The relationship between stressed and unstressed blood volume.

A. The dark fluid is the unstressed volume.
B. In sepsis the vasodilatation reduces the stressed volume and the venous return. The venous return can be restored by vasoconstriction or fluid administration.
Reproduced from Miller A, Mandeville J, (2016) Predicting and measuring fluid responsiveness with echocardiography. Echo research and practice 3: G1-g12, with kind permission from the author in accordance with the open access agreement.

A fluid bolus that is accommodated as unstressed volume does not increase CVP and does not challenge the heart to increase the SV. Epinephrine increases CO mainly by constricting the capacitance vessels in the splanchnic circulation, which leads to an increase in the stressed blood volume.

In conclusion, fluids are administered to increase CO. The heart may not respond in this way as fluids can be trapped as unstressed volume or leak out of the vessels or because the patient may not be able to respond to fluids due to a failing heart. In addition, the duration of increased SV after fluid bolus is short and returns to baseline within an hour following the administration of a fluid bolus (30).

2.4 SIDE EFFECTS OF FLUIDS

Fluid therapy is an important component of the treatment of septic shock. However, fluids do have negative effects. Fluids leak from the vessels and cause oedema in all tissues. Several studies have shown an association between fluid balance and mortality in patients in septic shock (31-34). However, it is uncertain whether the increased mortality is due to a higher fluid balance or if an increased need for fluids is simply a marker of illness severity. Even though all studies are adjusted for severity of illness in some way, there is still the possibility of residual confounding. There is one trial in which fluid boluses of 20–60 ml/kg or no boluses were given to Ugandan, Kenyan and Tanzanian children with septic shock; this showed that second day mortality was 10.6% in the albumin bolus group and 7.3% in the control group (35). The children were treated in paediatric wards and the results may not be generalisable to a setting where respiratory support is available. Nevertheless, it is a result that raises doubts about the beneficial effect of fluids.

Given that one clinical argument for giving fluids is to maintain renal perfusion and thus renal function, it may be surprising that a high fluid balance is associated with impaired renal function (36, 37). One reason why the kidney is more sensitive to fluid overload than other organs may be that it is encapsulated and therefore has a limited ability to accommodate volume changes (38). A regimen with more resuscitation fluids may lead to more problems with abdominal hypertension and abdominal compartment syndrome (39). It has long been known that fluid overload impairs weaning from mechanical ventilation (40, 41) . Fluid overload is also associated with lower levels of mobilisation following discharge from ICU (42).

2.5 FLUID ADMINISTRATION IN SEPSIS TODAY

Fluids, norepinephrine, dobutamine and RBC transfusion were the essence of the landmark trial of early goal-directed therapy (EGDT) by Rivers and colleagues. The EGDT protocol is described in detail in Fig. 4. The authors found a hospital mortality of 46.5% in the standard

care group and 30.5% in the EGDT group (43).

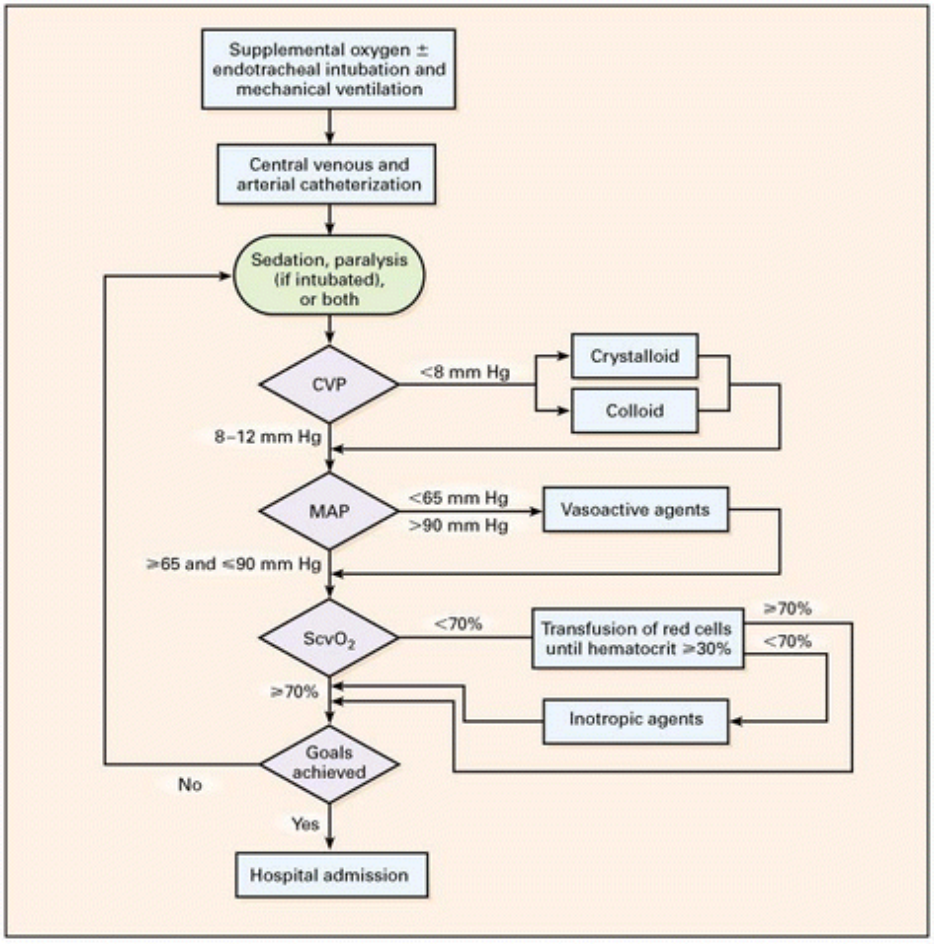

Fig 4. Protocol of early goal-directed therapy. The goals were CVP 8–12 mmHg, central venous oxygenation (ScvO2) ≥ 70%, MAP ≥ 65 mmHg and urinary ouput ≥ 0.5 ml/kg. 500 ml of fluids were administered every 30 min until the goal of CVP was fulfilled. Norepinehrine was administered if MAP was < 65 mmHg. RBC were administered if ScvO2 < 70% and haematocrite < 30%. If ScvO2 was < 70% and haematocrite > 30%, dobutamine was administered to increase CO.

Reproduced with permission from Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, Peterson E, Tomlanovich M, (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345: 1368-1377, Copyright Massachusetts Medical Society

It was a single-centre trial, and it has been criticised for lacking generalisability as the patients were severely ill when they arrived in the ER. This trial was the basis for sepsis guidelines for nearly 15 years. The trial was reproduced in three large trials, which found no difference in mortality between the EGDT groups the control groups (44-46). The recommendation from the Surviving Sepsis Campaign (SSC) is to initiate early fluid resuscitation with at least 30 ml/kg, and then more until the goals of CVP 8–12 mmHg, central venous oxygenation (ScvO2) ≥ 70%, mean arterial pressure (MAP) ≥ 65 mmHg and urinary output ≥ 0.5 ml/kg are achieved (47). One problem with this recommendation is the lack of an indication of how long it is to be followed. The EGDT protocol was used during

the initial six hours. In clinical practice, however, the recommendation can be used over the course of several days. This practice has led to huge resuscitation volumes. In the Vasopressin and Septic Shock Trial (VASST), in which either vasopressin or norepinephrine were given to patients with septic shock between 2001 and 2006, the mean cumulative fluid balance after four-days' volume was 11 +/- 8.9 l (31, 48). Another objection is that CVP does not predict fluid responsiveness (49). The published association between fluid balance and mortality has probably led to the ICU community reducing the amount of resuscitation fluids. For example, the amount of fluids given during the first 72 hours in the three recent EGDT trials were significantly lower than those in Rivers and colleagues' trial (50) .

2.6 CAN THE NEED FOR FLUIDS BE EVALUATED PRIOR TO FLUID ADMINISTRATION?

2.6.1 Evaluation of need for fluids using standard clinical signs

The fluid bolus strategies used in ICUs were recently investigated in a global cohort study (51). The main reason for fluid administration were hypotension (59%), oliguria (18%) and weaning from vasopressors (7.1%). Astonishingly, the result of the first bolus did not impact the prescription of the next bolus. In a French study, the median volume of fluid boluses during 96 hours of shock was 1.5 l (IQR 1.0 - 3.0) (52). Advanced haemodynamic monitoring to guide the fluid bolus was only used in 23.6% of the fluid bolus situations. The main reasons for fluid administration were hypotension (79%), oliguria (49%), high pulse rate (29%), skin mottling (25%) and high lactate (19%). There seems to be a discrepancy between the rationale behind administering fluids to patients who are fluid responsive and clinical practice. It is difficult to predict fluid responsiveness from standard haemodynamic parameters such as heart rate, blood pressure and urinary output (1). The adequacy of physicians' estimations of CO was assessed by Perel et al. They compared expected values with measured values of cardiac output in patients who were soon to be monitored by transpulmonary thermodilution (TPTD). The Bland-Altman plot between expected and measured CO values showed a bias of -1.54 l/min and the limits of agreement were -5.8 to 2.6 l/min. The physicians tended to underestimate high values and overestimate low values (53).

2.6.2 Passive leg raising test

Dynamic parameters that test the position on the Frank-Starling curve through an increase/decrease in venous return can predict fluid responsiveness. Pulse pressure variation (PPV) and stroke volume variation (SVV) are examples of dynamic parameters that utilise the reduced preload and increased afterload for the right ventricle during mechanical inspiration. However, using them to reliably predict fluid responsiveness requires a regular heart rate and mechanical ventilation with a tidal volume $\geq$ 8 ml/kg (54, 55). It is rare that these requirements are met in critically ill patients (56). Passive leg raising (PLR) is a test that can predict fluid responsiveness with 85% sensitivity and 91% specificity if the PLR test is evaluated using continuous cardiac output monitoring. This is independent of regular rhythm

and mechanical ventilation. The ideal cut-off for fluid responsiveness is an increase in CO by ≥ 10% +/- 2% (57). It is preferably performed with an initial head-of-bed (HoB) elevation of 45° in order to increase the amount of blood in the legs. The HoB elevation is then decreased as the legs are raised to 45°. If CI then increases by 7–15%, the patient is considered fluid responsive (Fig. 5).

Fig. 5. The performance of the PLR test.

So far, the PLR test has been implemented in two clinical trials. Richard et al. performed an RCT comparing the effect of a PLR test on time to weaning from vasopressors with that of a CVP-guided algorithm in patients with septic shock (56). There was no statistically significant difference between the groups. The PLR group received significantly less daily fluids. Kuan et al. performed a trial lasting up to three hours in septic patients in the ER in which patients were randomised to receive either fluid boluses given until SVI increased by < 10% in a PLR test or standard care. There was no statistically significant difference in the percentage that reached a 20% lactate reduction in three hours in these groups (58). There was a pilot study performed by Chen et al. in which a PLR test was used to guide either fluid loading or targeted fluid minimisation through reduced input and increased output by diuretics/CVVHD, depending on the response (59). They used three parameters to determine fluid responsiveness: a decrease in PPV to < 13%, an increase in SVI difference by > 10% or decreased inferior vena cava (IVC) distension index to < 18%. Patients fulfilling two criteria were considered fluid responsive. It is unclear if a PLR test can be used to improve the outcome of septic patients.

2.7 THE IMPACT OF TIMING OF ANTIBIOTICS ON MORTALITY IN SEPSIS

A landmark retrospective study of the effect on mortality of delaying adequate antibiotic administration from the onset of hypotension in sepsis was published 2006 by Kumar et al. (60). The OR for hospital mortality was 1.12 (CI 1.103–1.136) for every hour of delay in the administration of adequate antibiotics. The average decrease in survival was 7.6% for every hour of delay. There was a linear relationship between the delay in the administration of adequate antibiotics in septic shock and mortality. Ever since the publication of this article, it has been stressed that early administration of antibiotics is of the highest priority in sepsis. The SSC recommends administering broad spectrum antibiotics within one hour of the recognition of severe sepsis and septic shock. The level of evidence according to the GRADE system (61) for this recommendation was estimated by the SSC to be 1B for septic shock and 1C for severe sepsis (47). A prospective cohort study of patients in the ER failed to confirm an increase in hospital mortality per hour of the delay in administering antibiotics. The overall mortality in that study was much lower than in the study by Kumar et al. and most patients received antibiotics within three hours of being triaged in the ER (62). Patients with sepsis need antibiotics, but determining who has sepsis and who has other life-threatening disorders is not always easy. Prescribing broad spectrum antibiotics to all haemodynamically unstable patients might lead to the unnecessary prescription of antibiotics, with a risk of increased antibiotic resistance.

3 AIMS OF THE THESIS

The overall intention was to explore what scientific support there is for the treatment of septic patients in terms of their fluid management and the timing of antibiotics and to investigate new tools that could help the clinician decide on the amount and timing of blood transfusion and fluid administration in septic shock. The specific aims were:

1. To evaluate the effects on mortality of blood transfusion at a lower versus a higher haemoglobin threshold among patients with septic shock.

2. To investigate the association between a cumulative fluid balance three days after randomisation in the intensive care unit (ICU) and 90-day mortality in patients with septic shock.

3. To assess whether haemodynamic optimisation using protocols based on haemodynamic monitoring reduces mortality in critically ill patients.

4. To implement passive leg raising as a new method of evaluating fluid responsiveness in patients with septic shock in the intensive care unit.

5. To describe the timing of antibiotics in a cohort of septic ICU patients.

4 ETHICAL CONSIDERATIONS

The involvement of humans in research projects requires considerable reflection. Two key questions have been: “Would I like my mother to participate in this research project?” and “Are the risks of participation outweighed by the possible gain from the trial?”

In the TRISS trial, some clinicians found it hard not to transfuse patients with, for example, known ischemic heart disease until their Hb was ≤ 7 g/dl. The trial was justified, however, as there is equipoise between harm and benefit for RBC transfusion at this Hb threshold. There were safety measures that ensured patients would receive RBCs in the event of current myocardial ischemia or bleeding.

In the PLR trial we chose to study severely ill patients (patients in septic shock) in order to include only those patients who would benefit from advanced haemodynamic monitoring. Being critically ill and subject to critical care is dangerous. Blood pressure monitoring via an arterial line is part of routine intensive care. Arterial cannulation carries a small, but not negligible risk of bleeding and occlusion of the involved artery. There is a risk of haematomas at removal of the catheter of 6.1%, bleeding of 1.6% and of serious ischemic events due to occlusion of 0.2% (63). Advanced haemodynamic monitoring with TPTD requires a femoral or axillary arterial line instead of a radial arterial line. We judged that the extra risk of randomising patients to advanced haemodynamic monitoring was acceptable.

Critically ill patients are more vulnerable than healthier patients. They depend heavily on the care provided and there is a risk of patients or relatives agreeing to participate because they erroneously believe they will receive better care. To avoid this, all patients and relatives received both written and oral information, informing them that their future care would not depend upon their participation in the trial. They also received information that they could withdraw from the trial at any time without explanation.

The Helsinki Declaration states that groups that are underrepresented in medical research should be provided appropriate access to participation in research. Swedish legislation makes it difficult to perform intensive care trials as delayed consent is not allowed and research involving drugs on unconscious patients is not allowed. Thus there is a risk that the vulnerable critically ill patients are excluded from the benefits of research.

Ethical approval has been obtained for the TRISS trial (Denmark H-3-2011-114, Finland NTO 1/2013, Sweden EPN 2011/1603-31/2 and Norway 2011/2270/REK Vest) and for the TRISS-Fluid Balance study (Sweden EPN 2015-168-32/2 and Norway 2011/2270/REK Vest). In Denmark and Finland, the post-hoc analysis did not require an amendment. The ethical approval for the PLR trial was EPN 2013/1337-31/2. The ethical approvals for study V were EPN 2010/1780- 31- 2 and EPN 2011/1915-32/2.

The clinical trials were registered at ClinicalTrials.gov (TRISS NCT01485315, PLR NCT 02301585). The meta-analysis was registered at PROSPERO (2015:CRD42015019539).

The clinical trials have been performed in accordance with the WMA Declaration of Helsinki (64).

5 METHODS

5.1 OVERVIEW OF METHODS

The studies were performed using quantitative methods. An overview of the study methods is presented in Table 1. **Study I** was a large multi-centre trial, my contribution to which was being responsible for the trial at Södersjukhuset. **Study II** was a cohort study; a post-hoc analysis of Study I. **Study III** was a systematic review and meta-analysis. **Study IV** was a single-centre clinical trial that ended as a pilot study. **Study V** was an observational cohort study.

Study	Design	Study Population	Aim	No of participants	Statistical Methods
I	RCT	Patients with septic shock and Hb ≤ 9 g/dl	To study the effect on mortality of a transfusion threshold of 7 or 9 g/dl in septic shock.	998	Logistic regression, χ^2, Wilcoxon signed-rank test
II	Cohort	Patients with septic shock and Hb ≤ 9 g/dl who survived and stayed in the ICU for three days or more	To investigate the association between the cumulative fluid balance and mortality in patients with septic shock.	841	Cox regression, χ^2, ANOVA
III	Meta-analysis	Critically ill patients	To assess whether haemodynamic optimisation by protocols reduces mortality in critically ill patients.	3323	Mantel-Haenszel random effects model
IV	RCT (pilot)	Patients with septic shock for < 12 hours	To implement a protocol based on a passive leg raising test in patients with septic shock	34	χ^2, t-test, ANOVA, Mann-Whitney U test
V	Cohort	Septic ICU patients	To describe timing of antibiotics in a cohort of septic ICU patients	210	Logistic regression, t-test, Mann-Whitney U test, Fisher's exact test

Table 1. Overview of study methods.

5.2 STUDY DESCRIPTIONS

Study I was a large international multi-centre RCT. Patients with septic shock and Hb ≤ 9 g/dl were randomised to a transfusion trigger of either 7 g/dl or 9 g/dl during their entire ICU stay or up to a maximum of 90 days. Exclusion criteria were life-threatening bleeding, acute coronary syndrome, acute burn injury, having already received RBC in the ICU, previous reactions to RBC transfusion, refusal to receive RBC transfusion, withdrawal from active treatment and lack of consent. The median age was 67 years and the median SAPS II was 51(IQR 42 - 62) in the lower threshold group and 52(IQR 44 - 64) in the higher threshold group. The main sources of sepsis were the lungs and the abdomen. The trial was performed in 32 ICUs in Denmark, Norway, Finland and Sweden from Dec 2011 to Dec 2013. See Fig. 6 for patient flow.

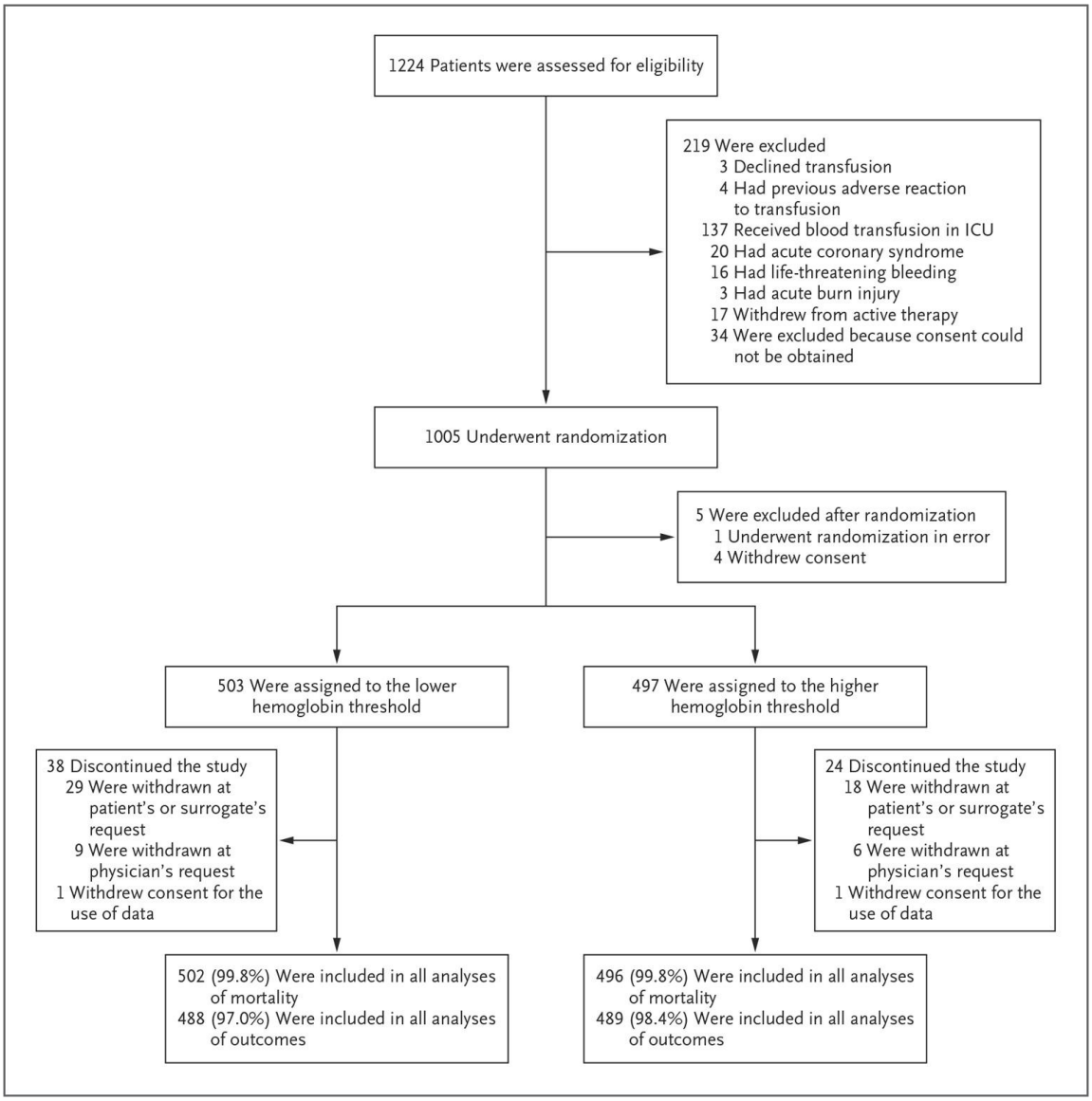

Fig. 6. Patient flow in the TRISS trial.

Study II was a cohort study, a secondary analysis of the TRISS trial. Patients who had been included in the TRISS trial, stayed in the ICU for ≥ 3 days, had complete fluid balance data and had given consent for use of the full dataset were grouped according to their fluid balance at the end of day 3. The study was performed from Jan 2014 to Oct 2015.

Study III was a meta-analysis. We evaluated the effect of structured haemodynamic protocols based on CO, SV, SVV, oxygen delivery, mixed venous oxygenation (SvO2) and ScvO2 on mortality in adult critically ill patients. We defined the meta-analysis by the Cochrane acronym PICO (participants, interventions, comparators, and outcomes). *Participants* were adult patients treated at an ICU, emergency department or corresponding level of care. The *intervention* had to be protocolised and based on results from haemodynamic measurements, defined CO, SV, SVV, oxygen delivery, ScvO2 or SvO2. *Comparators*: The control group had to be treated using the standard care, without any structured intervention based on the parameters mentioned above. Algorithms based only on CVP for evaluating fluid requirements were regarded as inefficient and control groups treated

in accordance with such were accepted. The selection of studies is described in a PRISMA flow diagram (Fig. 7). The study was performed from Dec 2014 to Jan 2016.

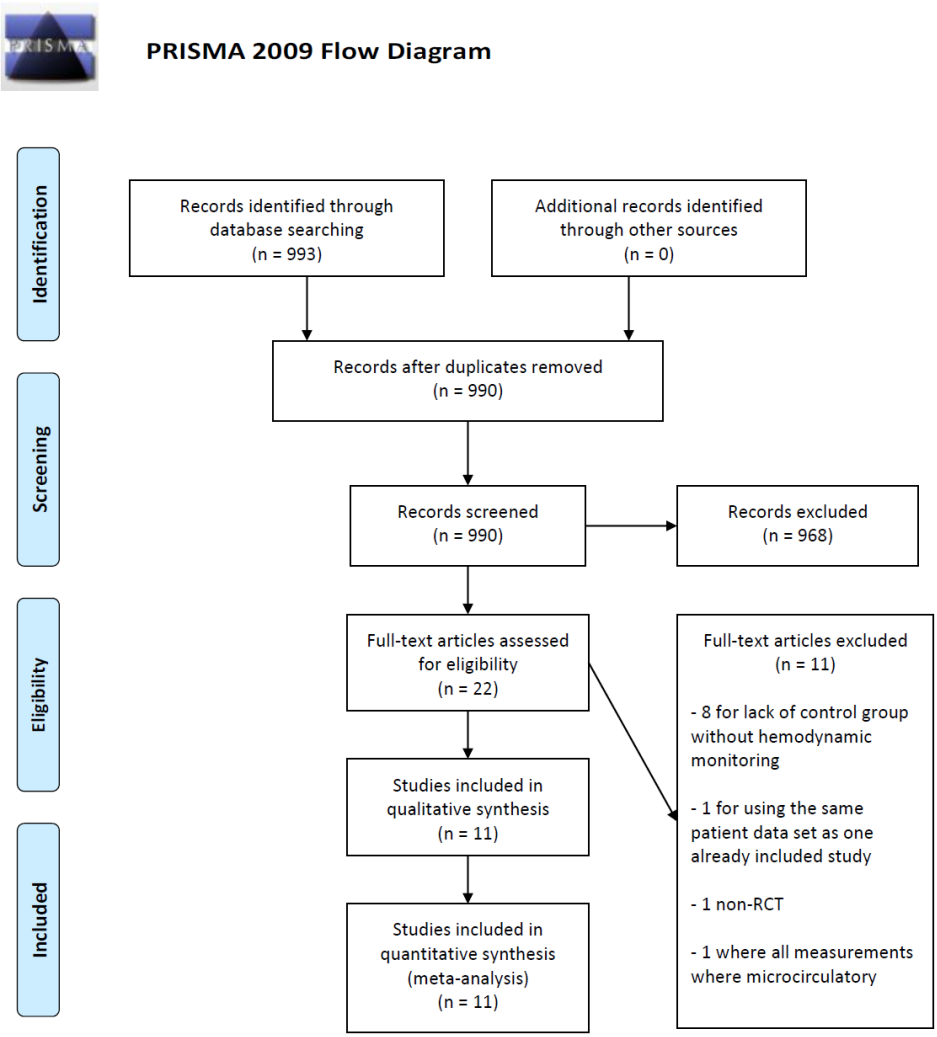

Fig. 7. PRISMA 2009 flow diagram for the meta-analysis.

Study IV was a pilot RCT. Adult patients with septic shock admitted to the ICU were randomised to a PLR test before every decision on resuscitation fluids or usual care. Exclusion criteria were >12 hours since the onset of septic shock, a contraindication to a femoral or axillary arterial line, a fracture of the hip or other pathology that would render the PLR test painful, femoral amputation, the clinical suspicion of elevated intra-abdominal pressure, an elevated intracranial pressure or imminent death (within 24 hours). The mean age was 71 +/- 11 in the PLR group and 67 +/- 15 in the control group. The primary source of infection was the abdomen (47.0%). The trial was performed in the surgical ICU at Södersjukhuset from Feb 2014 to Jan 2016. The patient flow in the PLR trial is described in Fig. 8.

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

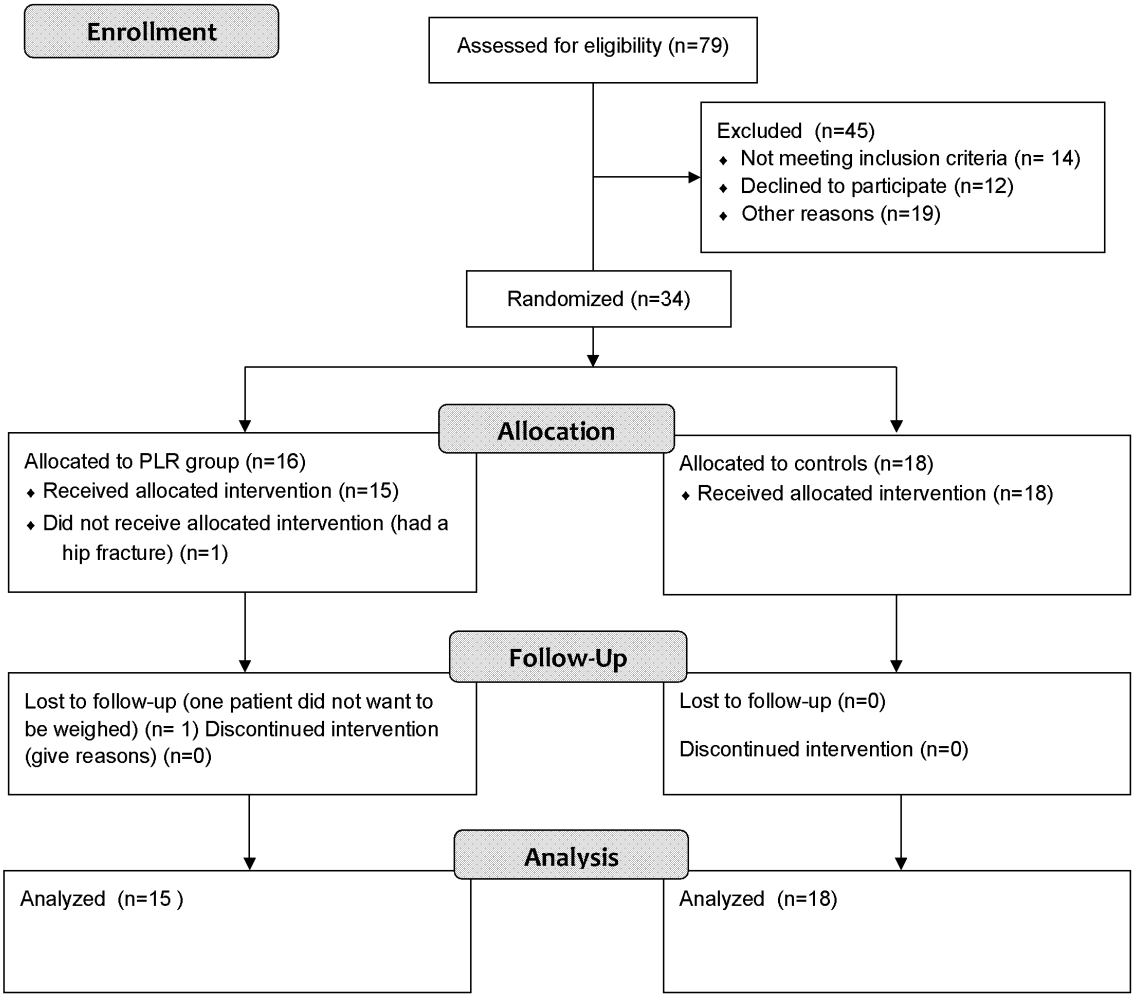

Fig. 8. CONSORT flow diagram for patient flow in the PLR trial.

Study V was an observational cohort study performed in four ICUs in Stockholm involving patients admitted to the ICU in the period 2005–2010. Patients who had been diagnosed with sepsis and stayed ≥ 4 days in the ICU, had been diagnosed with sepsis on arrival in the ER and had a known time for the first administration of antibiotics were included in the study (Fig. 9).

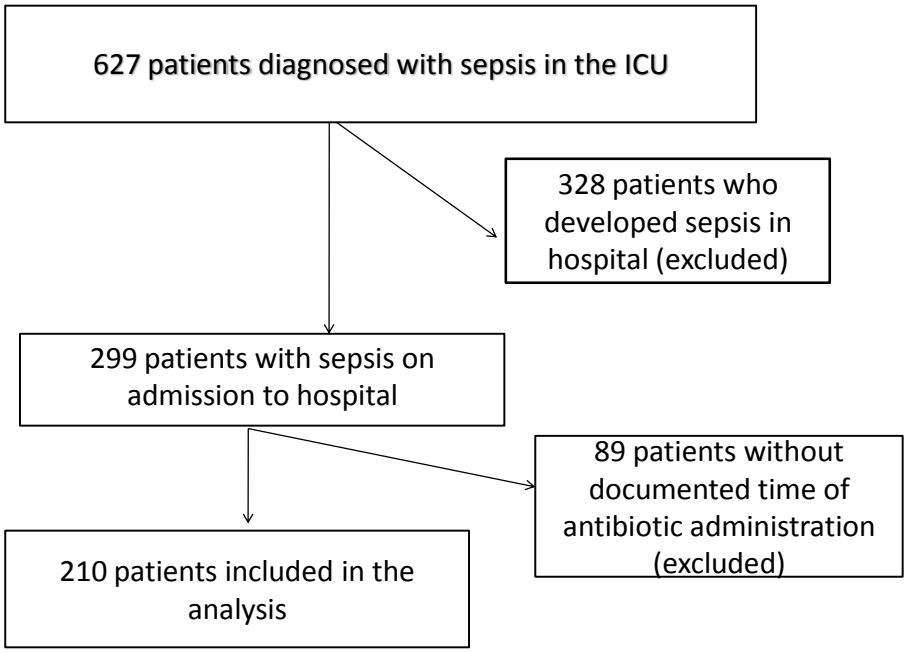

Fig. 9. Patient flow, Study V.

5.3 MEASUREMENTS AND DATA COLLECTION

In **Study I,** we measured Hb using a point-of-care blood gas machine (ABL 625, 700- and 800-series or ABL90 from Radiometer, Copenhagen, Denmark [31 ICUs] or Cobas b 221 from Roche Diagnostics, Rotkreuz, Switzerland [one ICU]). If an assigned transfusion level was reached, the patients received single units of cross matched, prestorage leukoreduced RBCs suspended in a saline-adenine-glucose-mannitol solution. Hb was then measured within three hours of the completed transfusion and additional RBCs were administered if required by the protocol. The clinical staff recorded the Hb and information about the transfused RBCs on paper. The researchers entered data concerning underlying diseases, laboratory values, fluid therapy, etc. into the online case report form (CRF). Ninety day mortality was gathered from patient files or regional and national registries.

In **Study II** we divided the population into four groups according to weight-adjusted cumulative fluid balance. The weight was the actual or estimated body weight used for dosing drugs. We had *a priori* decided on the groups: < 0 ml/kg, 0–29.9 ml/kg, 30–75

ml/kg and > 75 ml/kg. We chose < 0 ml/kg as we expected a negative fluid balance to be an advantage. Thirty ml/kg was a cut-off as this was the expected median based on data from Study I. An increased fluid balance of > 10% has previously been associated with increased mortality (37), hence the cut-off of > 75 ml/kg.

A team of five researchers gathered the data for **Study III** in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (65). We searched the PubMed, Embase and CENTRAL databases for articles using the following search terms: [("intensive care" OR "intensive care units" OR "ICU" OR critically ill OR critical illness OR emergency service OR emergency department) AND (cardiovascular agents OR fluid therapy) AND mortality]. The search was performed on 18 December 2014 with an updated search on 4 January 2016. Titles and abstracts were screened by two researchers. If there were differences of opinion, two more reviewers examined the article and consensus was reached after a joint discussion in the team. The articles included were read by a minimum of two researchers and data was collected using a data collection form customised from the standardised Cochrane Collaborative form. The risk of bias (ROB) in each trial was assessed by two researchers. As it is impossible to perform a blinded trial concerning haemodynamic management, we deviated from the recommendations in the Cochrane Handbook and our pre-planned analysis registered at PROSPERO (2015:CRD42015019539). Trials with a high ROB in the domain of blinding of participants and personnel and a low ROB in all other domains were regarded as having a low ROB. Otherwise the meta-analysis would not have contained any trials.

In **Study IV**, the patients in the PLR group received either a femoral or an axillary arterial line. The insertion was guided by ultrasound. They were monitored with PiCCO® (Pulsion medical systems, Feldkirchen, Germany) which gives a continuous CO by pulse contour analysis calibrated by TPTD (Fig. 10). Calibration with thermodilution was performed three times per day, or more if there were large fluctuations in the dose of norepinephrine.

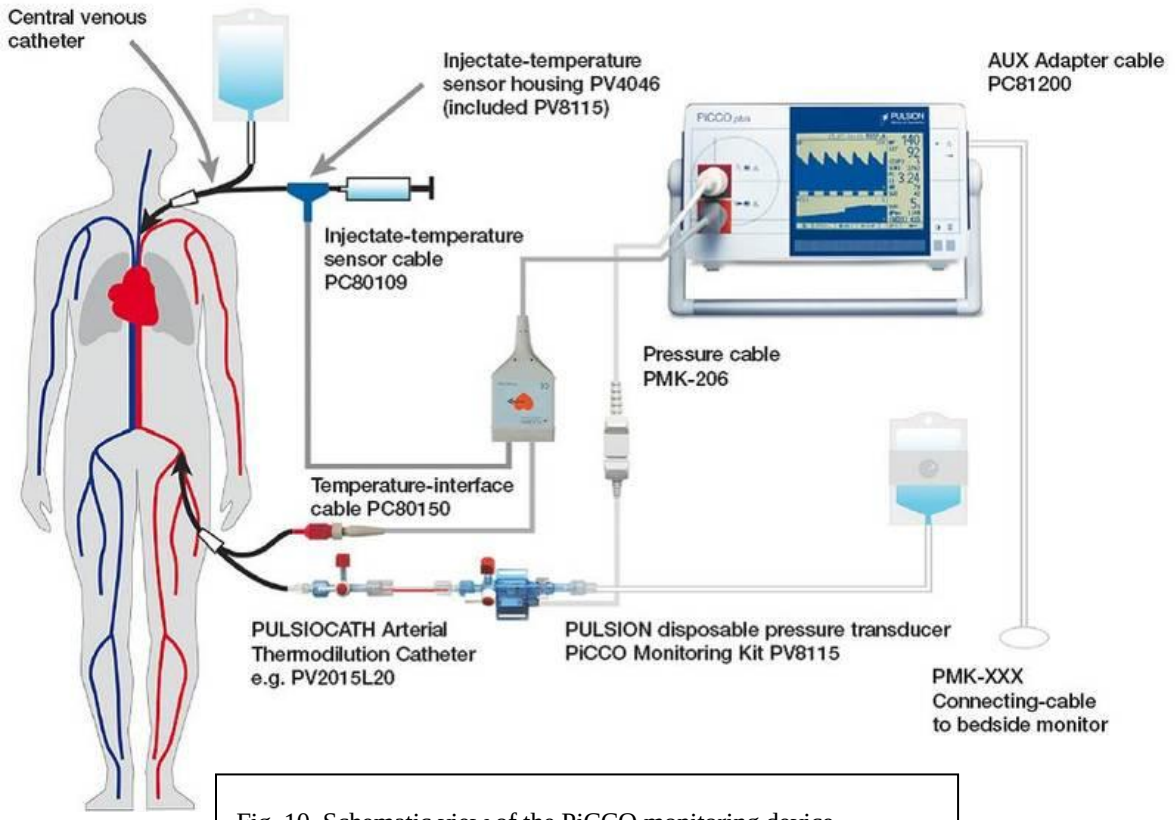

Fig. 10. Schematic view of the PiCCO monitoring device.
Reproduced with permission from Pulsion, Feldkirchen, Germany.

A PLR test was performed before every decision on resuscitation fluid administration, Fig. 11.

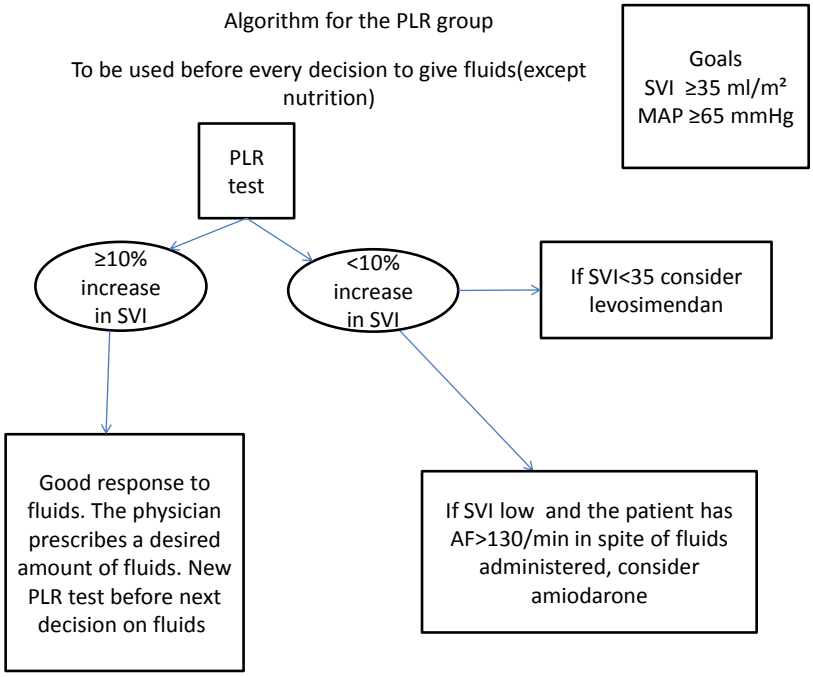

Fig 11. Haemodynamic algorithm for the PLR group.

We measured weight in the ICU bed (TotalCare SpO2RT®, Hill-Rom, Chicago, IL, USA) in the morning according to a standardised ward protocol. The accuracy of the bed scale was compliant with the EN45501 class 4, with a maximum permissible error of +/- 0.5 kg. If a patient was discharged from the ICU before the full three days, the ICU bed that had been used by the patient was transported to the ward and the patient was weighed by the researchers. The clinical staff screened and included patients in an electronic case report form (eCRF) that was linked to the electronic medical records. They also entered the haemodynamic variables from the PLR test. The researchers entered additional information concerning laboratory values and underlying diseases into the eCRF.

In **Study V**, we screened patients for inclusion if there was a diagnosis of sepsis in the electronic monitoring system (Clinisoft®, General Electric, Barrington, IL, USA). We gathered information about time of arrival to the hospital, time of first administration of antibiotics, comorbidities, etc. from the medical records. We used Statistics Sweden's Total Population Register to gather data on 90-day mortality.

5.4 STATISTICAL METHODS

In **Study I**, a statistician who was blinded to the allocation of the patients performed logistic regression on the modified intention to treat population (7 patients were deleted after randomisation; 6 due to withdrawal of consent and one because inclusion criteria were not met) with adjustment for the stratification variables (haematological cancer and study site). Odds ratios (OR) were converted to relative risks (RR). The RR were calculated for the pre-specified subgroups (chronic cardiovascular disease, age > 70 years and SAPS II > 53) with adjustment for the stratification variables .We analysed binary outcomes with the χ^2 test and ordinal data and rate with the Wilcoxon signed-rank test.

In **Study II**, we performed univariable Cox regression analysis with predefined covariates (age, sex, presence of haematological malignancy, site [sites with < 10 patients were grouped together], allocated Hb threshold, chronic cardiovascular or lung disease, source of infection, baseline SOFA score, highest plasma lactate in the 24 hrs before randomisation and acute/chronic RRT before randomisation). Variables with $p < 0.1$ were included in the final multivariable Cox regression model. The same variables were used to analyse the secondary outcomes. We compared categorical variables with the χ^2 test and continuous variables with the one-way ANOVA.

In **Study III**, we used the χ^2 statistics to assess statistical heterogeneity of treatment effect, where a p-value < 0.10 was interpreted as evidence of heterogeneity. We also used the I^2 statistics to assess the impact of statistical heterogeneity on the treatment effect. An I^2 of 0–40% was interpreted as indicating that the inconsistency might not be important. We chose the Mantel-Haenszel random effect model because the criteria for the fixed effect model were not fulfilled (same direction and size of effect in all studies). We had large clinical heterogeneity, which was another reason for choosing the random effects model. Effects

were presented as OR with a 95% confidence interval. We also performed a trial sequential analysis (TSA) to calculate the requested meta-analysis information size (IS)(66).

In **Study IV**, we analysed continuous normally distributed data with the independent samples t-test or ANOVA. We analysed continuous data with skewed distribution with the Mann-Whitney U test and categorical data with the χ^2 test. We performed intention-to-treat analyses.

In **Study V**, we estimated the association between late administration of antibiotics and 90-day mortality using multivariable logistic regression, adjusting for SAPS-3 score, gender and surgical sepsis. We analysed continuous normally distributed data with the independent samples t-test and continuous data with skewed distribution with the Mann-Whitney U test. We used Fisher's exact test for categorical data.

In **Study I**, we used SAS software, version 9.3 (SAS Software, SAS Institute Inc., Cary, NC, USA), and IBM SPSS Statistics software, version 17.0 (IBM Corp., Armonk, NY, USA) for statistical analyses. In **Studies II–V**, we used IBM SPSS Statistics software version 21 and 22 (IBM Corp., Armonk, NY, USA).

In all tests, $p < 0.05$ was regarded as statistically significant.

6 RESULTS, COMMENTS AND METHODOLOGICAL CONSIDERATIONS

The most important findings of the studies are presented here. For all results, please refer to the articles and manuscripts with appendices enclosed at the end of this book.

6.1 THE EFFECT OF TRANSFUSION THRESHOLDS ON MORTALITY

In **Study I**, the 90-day mortality was 43.0% in the low threshold group and 45.0% in the high threshold group, RR 0.94 (CI 0.78–1.09), $p = 0.44$. A lower Hb threshold led to fewer RBC transfusions; in the lower threshold group 1545 transfusions were performed, compared with 3088 in the high threshold group. There was no difference in the percentage of ischemic complications; 7.2% in the lower threshold group suffered from at least one ischaemic event, compared with 8.0% in the higher threshold group. It is important to note that it was more common to transfuse a patient who was above the Hb threshold in the low threshold group; 10% of patients in the low threshold group received RBC transfusions at an Hb above 7 g/dl, whereas this occurred in only 3% of the patients in the high threshold group. It was also more common for a patient in the high threshold group not to be transfused, in spite of their Hb being below the threshold (22% vs. 9% in the low threshold group). Consequently, the clinicians modified the protocol and made the differences smaller between the groups. However, the per-protocol analysis, which excluded patients who were transfused above their Hb threshold or not transfused below their threshold, showed a RR of 90-day mortality of 0.92 (CI 0.77–1.09) when adjusted for the stratification variables.

If there is no benefit, in terms of either reduced mortality or morbidity, to RBC transfusion at a higher Hb level, it is probably best to choose the lowest safe threshold. This involves reduced costs and fewer risks to patients. Many other trials performed in different settings have come to similar conclusions. In the TRICC trial, Hebert and colleagues randomised 838 critically ill patients to thresholds of 7.0 or 10.0 g/dl. There was no difference in 30-day mortality, but significantly more acute myocardial infarction (AMI) in the liberal group (0.7% in the restrictive and 1.2% in the liberal, p = 0.02) (23). In the FOCUS trial, patients > 50 years old with a history of cardiovascular disease and Hb < 10 g/dl after hip fracture repair were randomised to thresholds of 8.0 or 10.0 g/dl. The primary outcome was a composite variable of death or inability to walk across a room without human assistance at 60 days. There was no statistically significant difference in the primary outcome or in the rate of AMI between the two groups (67). In a trial of 921 patients with acute gastrointestinal bleeding who were randomised to an Hb threshold of 7.0 or 9.0 g/dl, there was an HR for death at 45 days of 0.55(CI 0.33–0.92) in the restrictive group. There were significantly more bleeding episodes in the liberal group (16% vs. 10%) (68). Following these trials, 7g/dl has been implemented in the NIH guidelines as the optimal Hb threshold in non-bleeding patients (69).

However, there may be objections to this interpretation of the study results. The risk of a type II error was 20%. This is level of uncertainty usually accepted in clinical trials, although it could be argued that it ought to be lower (70). It is a weakness that we did not systematically evaluate for the clinically relevant signs and symptoms of myocardial ischemia. Consequently, we may have missed an increased incidence of AMI. A meta-analysis of trials comparing restrictive and liberal transfusion triggers in patients with acute and chronic cardiovascular disease showed no increase in mortality, but a risk ratio of 1.78(CI 1.18–2.70) for acute coronary syndrome in the restrictive group. The authors suggest that a transfusion trigger of 8 g/dl be used in patients with cardiovascular disease (71). The main objection to the study design, however, has been that administering RBCs in accordance with set transfusion triggers is not physiological. The main reason for administering RBCs to septic patients ought to be to increase oxygen uptake in the cells. It would then be more reasonable to administer RBCs to patients who had inadequate oxygen supply, displayed as low ScvO2 or high blood lactate. However, there was no mortality benefit from RBC transfusion in response to low ScvO2 in the context of three large EGDT trials (44, 46, 72). A common problem with intensive care RCTs is patient selection. The population included is often highly selective and not representative of the entire ICU population. In the TRISS trial, however, there were few exclusion criteria. Other strengths of the trial are its size, the clear separation in Hb levels between the groups, the robust outcome variable (90-day mortality) and the fact that the study protocol reflects clinical practice in the ICU.

6.2 THE ASSOCIATION BETWEEN FLUID BALANCE AND MORTALITY

In **Study II**, we evaluated the 977 patients who had consented to our use of the full data set from **Study I**. There were 51 patients who died, 73 who were discharged and 7 had missing

fluid data. There were thus 841 surviving patients with ICU stays of at least three days and complete fluid data. The median cumulative fluid balance after three days was 2 480 ml (IQR 47 - 5 045). The 90-day mortality was 52%. In the univariable Cox regression we found that age, presence of haematological malignancy, site (sites with < 10 patients were grouped together), chronic cardiovascular or lung disease, source of infection, baseline SOFA score, highest plasma lactate in the 24 hrs before randomisation and chronic RRT before randomisation were associated with mortality ($p < 0.1$). After adjustment for these variables in the multivariable analyses, no statistically significant association could be found between fluid balance and mortality ($p = 0.37$), which is illustrated in a survival plot (Fig. 12). When comparing a cumulative fluid balance after three days of > 75 ml/kg with a negative fluid balance, the hazard ratio (HR) was 1.3 (CI 0.97–1.75).

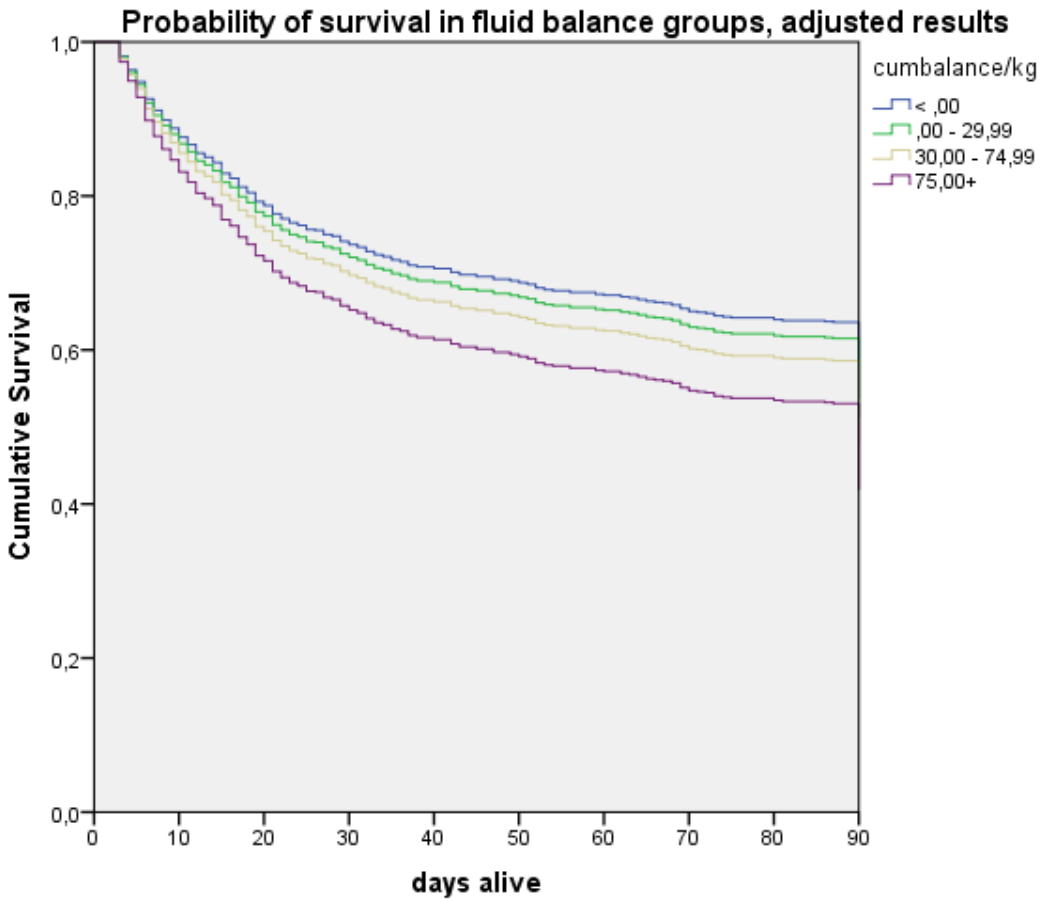

Fig. 12. Multivariable Cox regression survival plot for groups of cumulative fluid balance. The difference in mortality was not statistically significant, P = 0.37.

There are several cohort studies demonstrating an association between fluid balance and mortality (31-33, 73). The study populations, study size, covariates used for adjustment, cumulative fluid balance and ROB are illustrated in Table 2.

Study	Patient group	Patients n	Measurement of association	Cumulative fluid balance	Risk of bias
Boyd 2011	Septic shock	778	HR for 28 d mortality 0.47(CI 0.29–0.72) lowest compared to highest fluid balance group. Adjusted for age, APACHE II, dose of norepinephrine.	Mean cumulative fluid balance day 4; 11 l.	Post hoc analyses, potential selection bias with low screening/inclusion rate.
Vincent 2006	Sepsis, 15% septic shock	1177	OR for ICU mortality 1.1/litre increase in cumulative fluid balance (CI 1.0–1.1). Adjusted for SOFA and SAPS II.	Mean cumulative fluid balance day 3; 1.8 l.	Few patients in septic shock. Mean fluid balance was analysed as a continuous variable, which assumes a linear relationship between cumulative fluid balance and ln odds for mortality.
Micek 2013	Septic shock	325	OR for hospital mortality 1.66(CI 1.39–1.98) for highest fluid balance quartile day 8 compared to lowest. Adjusted for APACHE II, age, LVEF, vaso/inopressors, inappropriate antibiotics.	Median cumulative fluid balance day 24 hours non-survivors 4.4 l survivors 3.0 l.	Retrospective, single centre study. Age analysed as continuous variable.
Sadaka 2014	Septic shock	350	HR for hospital mortality 1.620 (95% CI, 1.197–2.043) highest 24-hour fluid balance compared to lowest. Categorised variables, Cox regression. Adjusted for age and SOFA score.	Mean cumulative fluid balance 24 hours 6.5 l.	Retrospective, single centre study.

Table 2. Associations between fluid balance and mortality in earlier cohort studies

It is difficult to compare the results from the cohort studies. They differ in terms of study population, disease severity, amounts of fluids and statistical methods. If few variables are used for adjustment, the risk of residual confounding is larger. One objection to the statistics used above (73) is that if fluid balance is analysed as a continuous variable; it is assumed that the relationship between fluid balance and OR for mortality is linear. From a physiological point of view, it is reasonable to believe that the relationship between fluid balance and mortality is U-shaped. It is probably harmful to receive both too little and too much fluids. Furthermore, it is unlikely that every increase in fluid balance is associated equally with

mortality. Another difference is that we analysed the fluid balance/patient weight. This should more adequately reflect the individual burden of fluid overload and thus the impact on mortality. One possible explanation why we did not demonstrate an association could be that the cumulative fluid balance in our cohort was relatively low. Fluid overload is perhaps only harmful above a certain level.

Our results are consistent with those of some previous studies. In a small observational study of 164 patients in septic shock, mortality was lower if the patients had received > 7.5 l of resuscitation fluids over three days (74). A large RCT comparing liberal and conservative fluid management in patients with acute lung injury showed a shorter time on a ventilator in the conservative group, but no difference in mortality (40).

The sample size of the study was too small to be able to exclude an association between fluid balance and mortality. The study had 60% power (post hoc calculation) to detect the crude difference in mortality of 8% between the two groups with the lowest fluid balance and the two groups with highest fluid balance.

Another important objection is the cohort study design. It is uncertain whether a positive fluid balance increases mortality or is simply a marker of illness severity. All we can discuss with a study like this is associations. Even though we adjusted for many possible confounders, we cannot exclude residual confounding. To answer the question of whether fluids increase mortality in septic patients, we would need an RCT in which patients were randomised to either a restrictive or a liberal fluid protocol.

6.3 PROTOCOLISED HAEMODYNAMIC MANAGEMENT IN CRITICALLY ILL PATIENTS

We included 11 trials in **Study III** (Table 3) (43-46, 58, 75-80) . We decided to disregard blinding because no trial was blinded to the personnel providing the treatment. All the included studies had a low ROB in the domain of blinding of outcome assessment as they evaluated mortality. There were 6 trials with a low ROB (Fig. 13). These trials involved 3 323 patients. The OR for mortality in the group with protocolised haemodynamic management was 0.94 (CI 0.73–1.22) (Fig, 14).

Table 3. Description of trials included in the meta-analysis

Values are presented as mean +/- standard deviation or as median (interquartile range). Abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation, ABSI = abbreviated burn severity index, CI = cardiac index, CVP = central venous pressure, DO_2I = oxygen delivery indexed to body surface, EVLWI= extra vascular lung water index, FTc = flow time corrected , ITBVI = intra thoracic blood volume index, MAP = mean arterial pressure, PAC = pulmonary artery catheter, PAOP = pulmonary artery occlusion pressure, PLR = passive leg raising, ScvO2= central venous oxygenation, SOFA = Sequential Organ Failure Assessment, SVI = stroke volume index, UOP = urinary output

Author and year	Location	Population	Type of monitoring	Haemodynamic protocol	Type of control protocol	No. of patients	Outcome
Kuan 2015	Singapore	Severe sepsis/septic shock patients	Bioreactance	Fluid bolus if PLR gave >10% increase in SVI	MAP, usual care by clinician	122	28-day mortality
Holm 2004	Germany	Burn unit patients	Transpulmonary thermodilution	Fluid boluses if ITBVI≤800 ml/m^2 or CI<3.5 l/minxm^2. Limited fluids if EVLWI>10 ml/kg	Treatment according to Baxter formula	50	Hospital mortality (secondary outcome)
Pearse 2005	Great Britain	ICU high risk surgical patients	Lithium indicator dilution	Fluid bolus to increase SVI>10%, Dopexamine to increase Do2I≥600 ml/minxm^2	MAP and CVP	122	60-day mortality
Chytra 2007	Czech Republic	ICU trauma patients	Oesophageal Doppler	250 ml colloid bolus if FTc<0.35 s until SV increased<10%	MAP and CVP	162	Hospital mortality (secondary outcome)
Jones 2010	USA	Septic shock patients	ScvO2	Crystalloid boluses to achieve CVP>8 mmHg and MAP>65 mmHg. RBC transfusion or dobutamine to achieve ScvO2≥70%	Lactate clearance	300	Hospital mortality
Rivers 2001	USA	Septic shock patients	ScvO2	Crystalloid boluses to achieve CVP>8 mmHg RBC transfusion or dobutamine to achieve ScvO2≥70%	MAP and CVP	267	Hospital mortality
Zhang 2015	China	Septic shock and/or ARDS patients	Transpulmonary thermodilution	Colloid boluses to achieve ITBVI≥850 ml/min/m^2	MAP and CVP	350	28-day mortality
Yealy 2014	USA	Septic shock patients	ScvO2	Crystalloid boluses to achieve CVP>8 mmHg. RBC transfusion or dobutamine to achieve ScvO2≥70%	Heart rate/systolic blood pressure or usual care	1 341	Hospital mortality at 60 days
Wheeler 2006	USA	ARDS patients	PAC	Fluid bolus if MAP<60mmHg and UOP<0.5 ml/kg/h or CI<2.5L/ minxm^2 and PAOP<18mmHg liberal, conservative 12 mmHg	Fluid bolus if MAP<60mmHg and UOP<0.5 ml/kg/h or mottling and CVP<8 mmHg conservative, 14 mmHg liberal	1 001	60-day mortality
Peake 2014	Australia & New Zealand	Septic shock patients	ScvO2	Crystalloid boluses to achieve CVP>8 mmHg. RBC transfusion or dobutamine to achieve ScvO2≥70%	Usual care	1 600	90-day mortality
Mouncey 2015	UK	Septic shock patients	ScvO2	Crystalloid boluses to achieve CVP>8 mmHg. RBC transfusion or dobutamine to achieve ScvO2≥70%	Usual care	1 260	28-day mortality

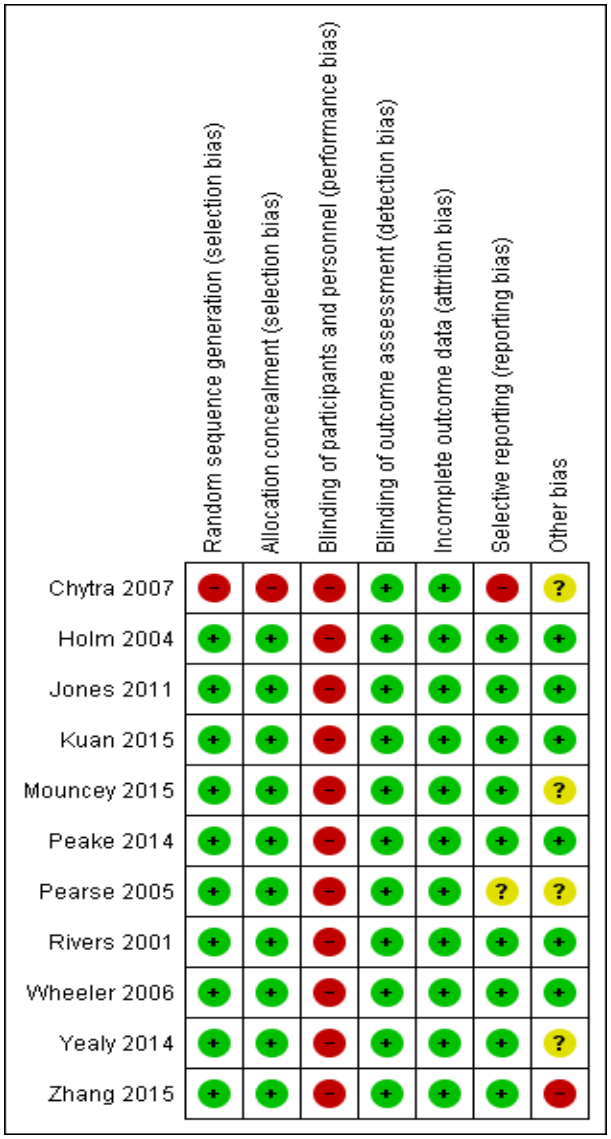

Fig. 13. Assessment of validity of included studies according to the Cochrane Collaborative Tool for Risk of Bias Assessment. + = low risk of bias, - = high risk of bias, ? = unclear risk of bias.

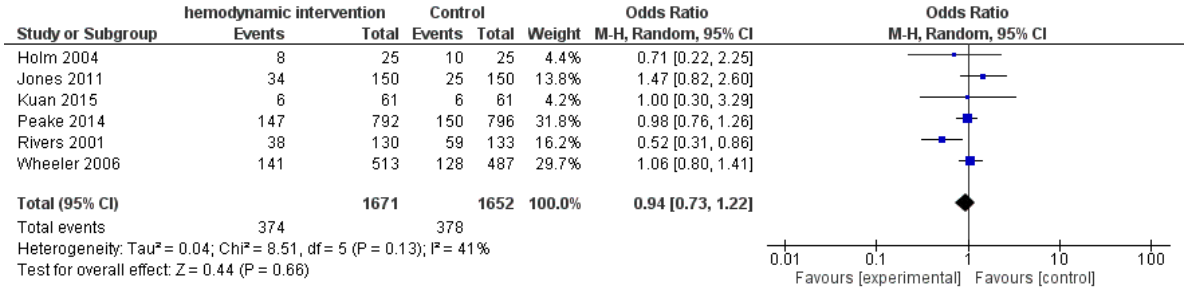

Fig. 14. Meta-analysis of effectiveness of hemodynamic monitoring combined with protocolised interventions to reduce mortality, low risk of bias trials. Weight is the relative contribution of each study to the overall treatment effect (odds ratio and 95% confidence interval) on a log scale assuming Mantel-Haenszel random effects model.

The trial sequential analysis showed that the estimated number of patients needed in order to exclude a positive effect with 80% power (the calculated IS) was 17 532 patients. We are therefore not able to exclude an effect on mortality using this meta-analysis. However, if the use of protocolised haemodynamic interventions does reduce mortality, the effect is likely to be small. Our results are in line with the results from a meta-analysis of EGDT trials, which did not show any reduction in mortality by using the EGDT protocol (81). Our results differ from an older meta-analysis performed before the new EGDT trials (82).

Haemodynamic management has been a cornerstone of intensive care ever since the development of the flow-directed PAC in 1970. Why have we not been able to successfully prove that the treatment we deliver is beneficial to patients? A meta-analysis of well-performed RCTs is supposed to provide the highest level of evidence. Nevertheless, if the quality of the included trials is low or the heterogeneity is large, the conclusions are uncertain. In order to evaluate the effect of protocolised haemodynamic management, the protocol must have a meaningful treatment goal, measurements must be correct, compliance with the protocol must be satisfactory and the control group must be treated using standard care. One problem with many trials is that they evaluate the effect of CVP-guided fluid therapy. CVP does not reflect fluid responsiveness (83). Neither do other static measures reflect fluid responsiveness. We only found three trials that evaluated the dynamic response to fluid (58, 76, 77). Kuan et al. performed a small trial without the intention of studying the effect on mortality. The other two were excluded from the analysis due to risk of bias. An inherent problem with haemodynamic trials is that it is impossible to blind the clinicians. Consequently, there is a substantial risk that the content of the protocol affects the treatment of the control group. This will reduce the effect of the investigated protocol. Critically ill patients are not a well-defined homogeneous group. It is hard to create a protocol that would suit every patient. It is possible that only the most severely ill patients really benefit from a structured approach and that their outcomes are drowned out by the information from the others. It might also be the case that a clinical judgment based on several signs indicating impaired perfusion (cold, mottled skin, high pulse rate, low blood pressure, low urinary output, high lactate) is better than a protocol based on one CO measurement. In conclusion, the optimal haemodynamic trial remains to be performed. It should be a trial with a dynamic measurement for evaluating fluid responsiveness, a reliable, safe haemodynamic measurement technique, a simple protocol that is acceptable to all clinicians and suitable for all patients and the trial size should be large enough to detect a clinically important difference in mortality.

6.4 ASSESSING FLUID RESPONSIVENESS IN SEPTIC PATIENTS USING A PLR TEST

Study IV was interrupted prematurely after the inclusion of 34/120 patients due to low weight gain in the control group. The power calculation was performed with the expectation of a weight gain of 8% of body weight in the controls and a reduction to a weight gain of 5% of body weight in the PLR group. In an interim analysis, we found that the mean weight gain

after three full ICU days was 0.6 (+/- 3.2) kg in the PLR group and 1.3 (+/- 3.9) kg in the control group (p = 0.59). The median amount of resuscitation fluid was 2 103 (IQR 1283 - 2 645) ml in the PLR group and 2 408 (IQR 954 - 5 045) ml in the control group, (p = 0.38). The median total amount of fluid was 10 646 (7 851 - 12 092) ml in the PLR group and 10 526 (6 158 - 12 902) ml in the control group (p = 0.67). Mean fluid balance was 1 566 (+/- 3 725) ml in the PLR group and 2 669(+/- 2 675) ml in the control group (p = 0.33). We interrupted the trial because the small difference in weight gain was not judged to be of clinical importance.

One possible reason for the low weight gain in the control group might be that the clinicians changed their pattern of fluid prescription during the study period. Maybe performing the study has made the physicians prescribe less fluid also in the control group. As the three large trials that tested the EGDT found that it did not reduce mortality, liberal fluid administration in septic patients has been called into question in the ICU community. This may have influenced the physicians' behaviour.

The study suffered from a low inclusion rate. Patients had to be included within 12 hours of the onset of septic shock. On-call clinicians might not have had time to include patient during the night as obtaining informed consent from relatives and initiating the PiCCO monitoring are time-consuming. If a patient was not included during the night, it was often too late to do so in the morning. Another PLR trial had similar problems with low inclusion rate (56). Sixty patients were included over 6 years. The main reason for not including eligible patients was time constraints for the physician. The CO monitoring ought to be non-invasive in order to make a PLR protocol more feasible. This would involve fewer risks to patients and less extra work for the attending physician. In a pilot trial, Chen and colleagues combined a PLR test with transoesophageal Doppler in intubated patients and transthoracic Doppler in non-intubated patients (59). They managed to include 82 patients in one year (medical ICU in a hospital with 1 250 beds). They also included a component of de-resuscitation with active fluid restriction and elimination in patients who were not fluid responsive. This is interesting because resuscitation fluids were, at least in our study, only a minor (1/4–1/5) part of the total amount of fluid administered. If fluid administration is to be reduced, it is probably important to reduce the administration of maintenance fluids and fluids for the administration of drugs, as well as resuscitation fluids.

The PLR test has been implemented in the emergency department with CO measured by bioimpedance (58). However, this measurement method has proven unreliable in validation studies (84). There were methodological weaknesses in our measurements too. According to the manufacturer, the accuracy of the bed scale was +/- 0.5 kg. In the clinical situation, an extra pillow or blanket might be left in the bed during the weighing procedure. There is therefore uncertainty regarding the point estimate of the outcome. The TPTD/pulse contour-derived measurements of SVI are also inexact. Many studies have found a clinically acceptable agreement between TPTD and PAC-derived thermodilution (85) using the proposed percentage error $\leq 30\%$. This is based on the assumption that a $< 20\%$ error for each

type of measurement is acceptable when estimating the CI (86). However, in a study comparing PAC to PiCCO in patients during off-pump cardiac surgery, the bias and limit of agreement between PAC derived CI and pulse contour CI was -0.07 +/- 0.92 l/min/m2, with a percentage error of +/- 33.5%. This was when the measurements were performed before calibration of the pulse contour CI. The authors conclude that safe use of the pulse contour CI requires that calibration be performed during surgery (87). It can be questioned whether it is possible to use a cut-off of 10% increase in SVI to decide on fluid administration after a PLR test when the precision of the PiCCO measurements is this low (88). However, the latest recommendations for the cut-off for fluid responsiveness are ≥ 10 +/- 2% increase in CO (57).

We were able to implement the protocol that prescribed a PLR test before every decision concerning the administration of resuscitation fluids, but the recruitment rate was low. We terminated the trial early as the weight gain was unexpectedly low in the control group. The protocol would have been more effective in a setting with a more liberal fluid administration. It would probably be better to protocolise the control group in order to make sure that the PLR protocol does not influence treatment in the control group.

6.5 TIMING OF ANTIBIOTICS IN A COHORT OF SEPTIC ICU PATIENTS

There were 64/210 (30%) patients who received antibiotics within one hour of their arrival in the emergency department. Median time to antibiotics was 38 (IQR 23 - 51) minutes in the early group and 211 (IQR 124 - 417) minutes in the late group. There was a lower proportion of women in the early group (28%) than in the late group (47%) (p = 0.015). There were more patients with surgical sepsis in the late group (25%) than in the early group (8%) (p = 0.004).The crude 90-day mortality was 28% in the early group and 31% in the late group (p = 0.75). After adjustment for SAPS 3 score, gender and surgical sepsis, there was no statistically significant association between antibiotic therapy later than one hour after arrival in the emergency department and 90-day mortality (OR 1.5, 95% CI 0.77–3.1). There are limitations with this study. Our sample size was too small to exclude an association between timing of antibiotics and mortality. The results cannot be generalised to the entire ICU population because only patients who stayed > 4 days in the ICU were included. There is a risk of selection bias as there might be patients suffering from sepsis who were not diagnosed correctly in the electronic monitoring system.

There are several studies supporting the importance of early empiric antibiotics (60, 89-93). Three of these are prospective studies (90, 92, 93). There are also some studies that do not show an association between timing of antibiotics and mortality (62, 94-98). Some of them are, however, small and too underpowered to show a difference in mortality (62, 95, 98). It is hard to compare results from cohort studies; populations and inclusion criteria vary and different definitions of the onset of sepsis are used. Even if there are attempts to control for confounding factors, there is always the risk of residual confounding.

As described in a recent meta-analysis and guideline from the National Institute for Health and Care Excellence, the timing of antibiotics in septic shock has not been investigated in

randomised clinical trials. The quality of evidence for the timing of antibiotics is very low. There was a significant reduction in all-cause mortality if antibiotics were administered within three hours (OR 0.70, CI 0.57–0.86). The recommendation, however, is that broad spectrum antibiotics should be administered within one hour in patients with a high risk of death from sepsis. There was no evidence of a difference between a delay of one hour and a delay of three hours (antibiotics within one hour compared to later, OR 0.87, CI 0.81–0.94) and the recommendation is that patients without organ dysfunction receive antibiotics within three hours. The group judged that the possible benefit of early administration of antibiotics would outweigh the risk of increased cost and increased resistance to antibiotics that this recommendation might lead to (99). Despite the low level of evidence, there is enough evidence that the early administration of adequate antibiotics is so important for patients in septic shock that it could not be evaluated in a RCT without a risk of patients being harmed. An important development will be the identification of microorganisms at the bedside. New ways of identifying microorganisms through molecular techniques are being introduced, for example IRIDICA, MALDI-ToF and others (100). These methods may significantly reduce the time taken to select the correct antibiotics and reduce the risk that resistance develops.

We found an unexpected gender difference in the timing of antibiotics. The SAPS 3 score was similar in men and women, thus the difference could not be explained by the men being more severely ill. This finding will need to be confirmed in a larger sample size, ideally among all septic patients in the emergency department.

In Swedish society, men and women have had equal rights since 1919 when women's suffrage was enacted. It is not obvious why women should receive antibiotics later than men. Many gender differences have been documented in previous studies. In a large Canadian study, more men (60%) than women (40%) were treated in intensive care, although about the same number of women as men were treated in hospitals. Women over the age of 50 were also less likely to receive invasive treatment in the ICU and were more likely to die after critical illness (101). In a large retrospective study of septic ICU patients in the US, Canada and Brazil, women were less likely to receive mechanical ventilation, more likely to receive a limitation in treatment and the hospital mortality was 35% for women, compared with 33% for men ($p = 0.006$) (102). In order to explore whether the threshold for ICU admission differed based on gender, two surveys containing patient cases in which the gender was changed but everything else was kept the same were distributed to Swedish clinicians. No difference was found in the rate of ICU admission between male and female cases in this survey (103). However, there was a low response rate and it is uncertain whether the responses are representative of the entire medical profession. In a large retrospective study based on the Swedish ICU registry from 2008–2012, encompassing 127 240 admissions, 43% were women and their SAPS 3 at admission was lower than that of the male patients. Male sex was associated with higher use of ICU resources (104). There are many studies indicating gender differences in the treatment of critically ill patients. In order to understand these differences, qualitative studies of the attitudes and behaviour of clinical staff and patients are needed.

7 GENERAL DISCUSSION

7.1 WEAKNESSES OF THE THEORY OF FLUID RESPONSIVENESS

The conventional way of increasing CO by giving fluids is firmly established in clinical practice. However, there are objections to the basic assumptions. A patient whose CO does not increase in response to fluids should not receive more fluids. But saying that a patient is fluid responsive is not the same as saying that there is a need for fluids. A patient who is fluid responsive does not necessarily benefit from fluid bolus therapy. The perceived benefit of filling patients with fluids until the heart is working on the flat part of the Frank-Starling curve is that this is an easy way to increase CO. Over the years, many protocols have been published the basic premise of which is reaching this level. This premise has been called into question (12), especially lately, as the risks of fluid overload have been highlighted. In the PLR protocol tested in **Study IV**, we only used the PLR test following a clinical decision to administer fluids. We used a lack of fluid responsiveness as a reason not to give fluids instead of using a positive PLR test as a reason to give fluids. Even if the patients fulfilled the clinical criteria for a fluid bolus and were fluid responsive in a PLR test, it is not certain that the fluid bolus therapy would lead to clinically important benefits.

The rationale behind increasing CO is to improve systemic oxygen delivery. However it is unclear whether improved systemic circulation leads to enhanced microcirculation (105). There are many things that we still do not know about microcirculation. It is possible to monitor the microcirculation under the tongue (106), but the device available is expensive and is only used for research purposes. The correlation between the circulation under the tongue and the intestinal circulation is not clear (107). It is also uncertain whether enhanced microcirculation leads to improved clinical outcomes. In a recent trial comparing a protocol based on correction of the microcirculation with a protocol based on systemic haemodynamic parameters, there was no difference in SOFA score between the two groups on day four (108). It is not yet possible to target microcirculation during resuscitation in clinical practice, but when striving to optimise the systemic circulation, one should keep in mind that the goal is optimised cellular oxygen delivery. It is possible that an increased CO is an irrelevant goal.

7.2 DIFFICULTIES WITH CLINICAL TRIALS IN CRITICALLY ILL PATIENTS

There is an ongoing debate in the ICU research environment about whether it is possible to perform a positive clinical trial in critically ill patients. Many recent large, well-performed trials have been neutral. There are many possible explanations for this; it may be that the treatment targets are incorrect. The statistical power is dependent on the baseline risk of death, the size and variability of treatment effect and the size of modifiable mortality in the study population (109). It is common to overestimate the mortality rate when calculating the sample size both because mortality rates in sepsis are reported to be declining (110) and as patients who are at imminent risk of death are commonly excluded from trials. Sepsis is a syndrome with many complex pathophysiological pathways. It is thus unlikely that one single intervention could influence all-cause mortality. There is a large heterogeneity in population baseline risk of death in sepsis trials, which will lead to a wide variability in the possible

benefit from the studied intervention. In a neutral trial, there is a risk that there might be a high-risk group that consistently benefitted if there is not perfect collinearity between treatment harm and effects. It is also possible to have a positive trial in which one group was actually harmed (111). There are exceptions from the experience of neutral clinical trials. The 6S trial showed increased mortality in patients with severe sepsis randomised to hydroxyethyl starch compared to Ringer's acetate (112). This trial has significantly reduced the use of hydroxyethyl starch in septic patients (51). Another example of a recent large RCT that changed treatment recommendations was the Sepsis Occurrence in Acutely Ill Patients (SOAP) II trial, which compared norepinephrine to dopamine in septic shock. There was no statistically significant difference in mortality, but there were twice as many arrhythmias in the dopamine group (113). Norepinephrine is now recommended as the first line drug in septic shock (47).

Clinical researchers are looking at outcomes other than mortality, e.g. clinical composite end-points, with mortality retained as a safety assessment (109). Another suggestion is presenting mortality stratified by quintiles of baseline risk of death (111). If we want to detect small differences in mortality, large trials are needed. Cluster-randomised trials have been suggested as a way of performing larger studies. Registry-based trials are another way of making large trials possible (114). Individual patient data meta–analyses have also been attempted, for example with the three large EGDT trials (clinicaltrials.org NCT02030158). The way forward is unclear; all of these methods will probably be tested in the quest to increase our knowledge and improve clinical practice and outcomes for septic patients.

7.3 CLINICAL IMPLICATIONS

It is safe to adopt a Hb threshold of 7 g/dl in septic ICU patients except in patients with pre-existing cardiovascular disease for whom a transfusion threshold of 8 g/dl is suggested. This reduces the number of RBC transfusions and the risk of complications from transfusion.

It is still unclear whether fluid overload increases mortality. According to the Centre for Evidence Based Medicine scale (115), the level of evidence available is 2b, with this being individual cohort studies suggesting possible harm from fluid overload. While we wait for the results of RCTs, fluids should be regarded as drugs. Accordingly, fluids should not be prescribed without a clear indication and the intended effect should be weighed against possible side effects.

There is no haemodynamic protocol that has been shown to consistently reduce mortality. As clinicians, we are left to support the circulation of our patients as best we can. One clinical recommendation concerning the administration of fluids in septic shock could be to monitor cardiac output in patients who cannot be stabilised by initial resuscitation. The response to fluids may be assessed subsequently using a PLR test, after which fluid administration may be reduced for those patients who are fluid responsive. This is in line with the latest European Society of Intensive Care Medicine task force recommendations:

> ‘We recommend measurements of cardiac output and stroke volume to evaluate the response to fluids or inotropes in patients that are not responding to initial therapy. Level 1; QoE [quality of evidence] low (C) […] We recommend using dynamic over static variables to predict fluid responsiveness, when applicable. Level 1; QoE moderate (B). When the decision for fluid administration is made we recommend to perform a fluid challenge, unless in cases of obvious hypovolemia (such as overt bleeding in a ruptured aneurysm). Level 1; QoE low (C). We recommend that even in the context of fluid responsive patients, fluid management should be titrated carefully, especially in the presence of elevated intravascular filling pressures or extravascular lung water. Ungraded best practice.’(12).

The most up-to-date recommendation concerning the timing of antibiotics in septic patients is that published by the National Institute for Health and Care Excellence in 2016. This recommendation is that broad spectrum antibiotics should be administered within one hour in patients with high risk of death from sepsis. Patients without organ dysfunction should receive antibiotics within three hours. The group considered the overprescription of broad spectrum antibiotics that this recommendation might bring about, and judged that the possible benefit of early administration of antibiotics would outweigh the risk of increased cost and increased resistance to antibiotics (99).

7.4 FUTURE RESEARCH

7.4.1 Haemodynamic effects of fluid therapy

There are basic questions concerning fluid therapy in septic patients that need to be answered. Clinicians administer fluids in order to correct hypotension, tachycardia, oliguria and poor tissue perfusion. It is unknown to what extent these goals are fulfilled by the administration of fluids. The expected and actual effects of fluid administration in septic patients need to be studied in order to help clinicians make better-informed decisions about how to administer fluids.

In the ER and the operating theatre fluids are often warmed to body temperature when large volumes are administered. In the ICU, fluids are usually administered at room temperature. Because room temperature fluids are colder than the patient, this may cause sympathetic mediated arterial vasoconstriction and a consequent rise in blood pressure, but diminished peripheral perfusion (116). It would be interesting to know if parts of the haemodynamic response to fluids could be due to cooling.

7.4.2 Alternatives to current fluid administration in septic shock

In sepsis, vasodilatation is the main reason for hypotension. A rational approach would be to administer vasopressors at an early stage, provided no fluid has actually been lost. One important question is how much fluid should be administered before the initiation of vasopressors. The SSC guidelines recommend at least 30 ml/kg over the first three hours, but there is no direct evidence to support this recommendation (47). One obstacle to early

administration of vasopressors is that it is a long-standing practice that norepinephrine has to be administered through a central line, which (in Sweden) is not usually available until the patient is admitted to the ICU. A peripheral line is shorter (usually 2.5–4 cm) and the risk of displacement is higher than with a central line (15–25 cm). A displaced line could lead to extravasation of norepinephrine, which might lead to necrosis. A recent trial showed that norepinephrine could be administered safely via a peripheral line (117). However, this was performed using a very rigorous protocol in an ICU. The safe use of peripheral norepinephrine in the emergency department and the operating theatre needs to be studied, as does the minimum amount of fluid that should be administered before the initiation of norepinephrine.

Studying the impact of restrictive as opposed to standard fluid therapy on mortality, maintenance fluids included, is a high priority.

7.4.3 Evaluation of individualised goals for resuscitation

In the future, when there is a non-invasive CO monitoring device that is both accurate and precise, there may be time to perform a PLR trial with a haemodynamic protocol similar to ours. It could then be argued that it is possible to use delayed informed consent as there would be minimal risk to the patients. The inclusion rate might then be improved, making a large-scale trial feasible. It is important to continue studying haemodynamic optimisation. As expressed in the conclusion of a recent Cochrane review of the use of vasopressors in septic shock:

> ‘In the light of current evidence, additional well-designed studies with individual goals of resuscitation including clinical parameters of end-organ perfusion and appropriate patient-relevant outcome end points are urgently needed’ (118).

Different resuscitation targets have been proposed. The difference between central venous and arterial PCO_2 ($\Delta PavCO_2$) increases when microcirculation is impaired. It has been suggested that a combination of ScvO2 and $\Delta PavCO_2$ could be used to detect patients with impaired microcirculation despite normalised ScvO2 (100). Another possible haemodynamic goal could be to keep the CVP low instead of high. The organ blood flow is determined by the difference between MAP and CVP and the resistance to flow. A high CVP has been shown to be associated with acute kidney injury (119). An algorithm to reduce CVP would perhaps increase renal blood flow and decrease the incidence of acute kidney injury.

7.4.4 Reducing leakage from blood vessels by protecting the glycocalyx

The role of the glycocalyx is described in a modified Starling model (120). It would be interesting to find a way to reduce the endothelial damage in sepsis. Experiments have been performed in which albumin protects the glycocalyx (121) . Early administration of albumin to protect the glycocalyx has not been tested in patients. The challenge lies in administering the albumin before the glycocalyx is damaged as the autonomous adrenergic reaction to low blood pressure damages the endothelium at an early stage. It would be interesting to study

whether administering albumin in the ambulance to patients with suspected infection and hypotension protects the glyocalyx and reduces leakage from vessels.

7.4.5 Gender differences in the treatment of septic patients

Female gender was associated with later administration of antibiotics. A prospective study that includes all patients with sepsis should be performed in the emergency department setting. If the difference in timing of antibiotics between men and women persists, the reasons for this should be investigated using qualitative studies of attitudes among patients, relatives and healthcare personnel. Possible explanations for a gender difference in the timing of antibiotics are that women present symptoms differently when they have sepsis and organ dysfunction. Women are perhaps less likely to complain. Another possibility is that healthcare personnel act differently when caring for men than when caring for women.

7.5 REFLECTIONS CONCERNING LEARNING OUTCOMES

There are many things that have been important to my development as a researcher. I will describe some of the key elements. A fellow doctoral student and I have held monthly journal clubs in order to learn to critically appraise literature. I have attended research courses where I have learned about legislation, ethics and statistics. I have also learned that in research, things do not always turn out the way you expected. I started conducting a registry based study because I thought that the data-gathering phase would be short. It turned out to be impossible to obtain the data I needed. Instead of being a short cut to learning about analyses and writing, it was a circuitous route. Through research collaboration and visits to Copenhagen and Melbourne, I have had the opportunity to learn from clinical researchers how to plan and run clinical ICU trials. I have learned that high quality ICU research is best done in collaboration between ICUs.

8 CONCLUSION

The scientific support for how clinical fluid management in patients with septic shock should be performed is poor. More research is needed in order to show whether reducing fluid overload can decrease mortality. In the meantime, fluids should be treated as drugs and should not be prescribed without a clear indication. The intended effect should be weighed against possible side effects.

- It is safe to adopt a Hb threshold of 7 g/dl in septic ICU patients except in patients with pre-existing cardiovascular disease for whom a transfusion threshold of 8 g/dl is suggested.
- It is uncertain whether fluid overload is associated with mortality at median cumulative fluid balance of 2.5 l on day three.
- It has not been proven that protocolised haemodynamic management improves outcome.
- It was possible to use the protocol based on a PLR test, but the recruitment rate was low. The weight gain was low in both the PLR and the control groups.
- Female patients and patients with surgical sepsis were overrepresented in the group that received antibiotics after more than one hour in the emergency room. We could neither confirm nor exclude a survival benefit from early administration of antibiotics.

9 SUMMARY OF THESIS IN SWEDISH

9.1 BEHANDLING AV PATIENTER MED BLODFÖRGIFTNING-VÄTSKA, BLOD OCH TID TILL ANTIBIOTIKA

Bakgrund: Blodförgiftning, eller sepsis, är när en infektion leder till en okontrollerad immunologisk reaktion som i sin tur leder till skada på livsviktiga organ. Vätska borde, utifrån ett fysiologiskt resonemang, ges till patienter med sviktande cirkulation för att öka hjärtminutvolymen och därmed leveransen av syrgas till kroppens vävnader. Det är dock endast hälften av kritiskt sjuka patienter som ökar sin hjärtminutvolym efter tillförsel av vätska. Läkare förskriver vätska för att korrigera lågt blodtryck, hög puls, låg urinproduktion och dålig perifer genomblödning. Dessa parametrar kan inte förutsäga om en patient kommer att svara på vätska med en ökad hjärtminutvolym. Internationella riktlinjer säger att patienter med blodförgiftning och sviktande cirkulation ska få minst 30 ml vätska/kg kroppsvikt. Det finns inga riktlinjer för när vätsketillförseln bör minska. Detta har lett till övervätskning av patienter med blodförgiftning. Det finns många observationsstudier som visat på en association mellan övervätskning och dödlighet. Svagheten med dessa studier är att de inte kan berätta om vätskan är orsaken till den ökade dödligheten, eller bara ett tecken på att de patienter som fick större mängd vätska var sjukare. Patienter med blodförgiftning och blodbrist får ibland röda blodkroppar för att säkerställa att kroppen får tillräckligt med syre. Det finns risker med att ge röda blodkroppar, som övervätskning, immunologiska reaktioner och infektioner. Trots tidigare studier är det osäkert vid vilken Hb-gräns som patienter med blodförgiftning ska få röda blodkroppar. Det finns studier som visat ett starkt samband mellan tid till antibiotika vid blodförgiftning med sviktande cirkulation. Internationella riktlinjer rekommenderar att antibiotika ska ges inom en timme från att cirkulationssvikt diagnosticerats.

Studie I var en klinisk studie där patienterna lottades till Hb-gräns för blodtransfusion på 70 eller 90 g/l. De som hade Hb 70 g/l som gräns fick påtagligt mindre blod. Det var ingen skillnad i dödlighet efter nittio dagar eller i antal hjärtkomplikationer. Studien visar att det är säkert att använda sig av 70 g/l som Hb gräns vid blodförgiftning med cirkulationspåverkan, vilket stämmer överens med studier som undersökt andra patientgrupper. En senare metaanalys har visat att patienter med kronisk hjärtsjukdom bör ha Hb 80 g/l som gräns för transfusion.

Studie II undersökte sambandet mellan vätskebalans efter tre dagar på IVA och dödlighet efter 90 dagar i studie I. Medianvärdet för vätskebalansen efter tre dagar var +2,5 l. Det fanns inget statistiskt säkerställt samband mellan vätskebalans och dödlighet efter korrigering för faktorer som kunde förväntas påverka både dödlighet och hur mycket vätska patienterna fick. Detta står i kontrast till vad som visats i många andra studier. Skillnaden skulle kunna bero på att våra patienter hade en lägre ackumulerad vätskebalans än vad patienter haft i tidigare studier, eller att övervätskning blir farligt först efter en viss mängd. Dock var patientantalet något för litet för att vi säkert skulle kunna utesluta att övervätskning på denna nivå var associerad med dödlighet.

Studie III var en metaanalys av studier som undersökt effekten på dödlighet av att använda ett hemodynamiskt schema hos kritiskt sjuka patienter. Vi använde protokollet i Cochranes handbok för systematisk genomgång av interventioner. Vi krävde att det hemodynamiska schemat skulle vara grundat på hjärtminutvolym, slagvolym, slagvolymsvariation, syrgasleverans, centralvenös syremättnad eller blandvenös syremättnad. Kontrollgruppen fick inte ha någon sådan mätning. Vi inkluderade elva studier. Av dessa var det bara sex som höll en kvalitet som levde upp till Cochranes krav på låg risk för systematiska fel. Det var ingen statistiskt säkerställd minskning av dödlighet i grupperna som behandlats enligt ett hemodynamiskt schema. Antalet patienter var dock för få för att vi skulle kunna utesluta att avsaknaden av en skillnad hade uppkommit av en slump. Dessutom är det avgörande att rätt mål tillämpas i ett hemodynamiskt schema. Bara en av de sex studierna använde ett dynamiskt mått på svar på vätska. Slutsatsen är att det finns för litet underlag för att uttala sig om huruvida ett hemodynamiskt schema kan påverka dödligheten.

Studie IV var en klinisk studie där patienter på intensivvårdsavdelningen med blodförgiftning och cirkulationspåverkan lottades till ett hemodynamskt schema grundat på resultatet av ett benlyftstest eller vanlig behandling. Benlyft gjordes om läkaren, baserat på klinisk bedömning, trodde att patienten behövde vätska. Om slagvolymsindex ökade med 10% eller mer vid benlyft tolkades detta som att patienten kunde svara på vätska och läkaren fick då ordinera önskad mängd vätska. Om slagvolymsindex ökade med <10% fick ingen vätska ges. Syftet var att se om användandet av detta hemodynamiska schema skulle leda till minskad viktuppgång. Vi hade planerat en studiestorlek på 120 patienter, baserat på en förväntad viktuppgång på 8% av kroppsvikten. Efter en interrimsanalys visade sig viktuppgången i kontrollgruppen vara betydligt lägre än beräknat. Vi valde att avsluta studien i förtid pga att vi bedömde att viktuppgången i kontrollgruppen var för liten för att vara av betydelse för patienterna.

Studie V var en journalstudie av tid från ankomst till akuten till antibiotika och dödlighet efter nittio dagar hos patienter som vårdas för blodförgiftning på IVA. Trettio procent fick antibiotika inom en timme. Kvinnor fick antibiotika senare än män.

Slutsats: Det finns bristande vetenskapligt stöd för hur vätskebehandling vid blodförgiftning ska göras. Det behövs kliniska studier som jämför restriktiv med liberal vätskebehandling för att se om dödligheten kan minska genom minskad övervätskning.

Klinisk tillämpning: Vid blodförgiftning bör Hb 70 g/l användas som gräns för transfusion om patienterna inte har pågående hjärtinfarkt. Patienter med kronisk hjärtsjukdom bör dock ha Hb 80 g/l som gräns för transfusion. Vätska bör inte ges utan att den förväntade effekten vägs mot möjliga negativa effekter. Ett expertråd är att patienter som inte initialt stabiliseras av vätska bör övervakas med mätning av hjärtminutvolym. Då är det möjligt att med ett benlyftstest avgöra om patienten kommer att svara på vätska med ökad hjärtminutvolym.

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